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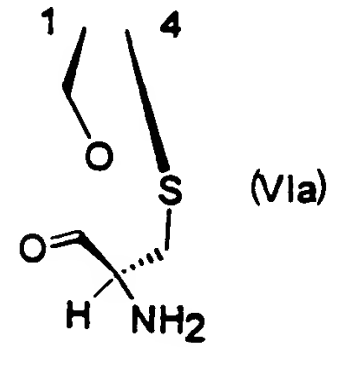
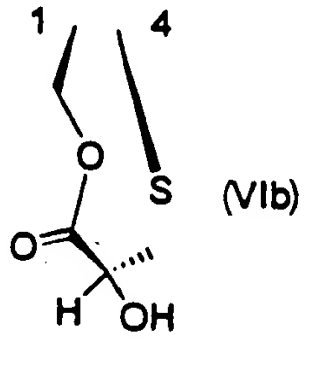
(54) Title: ANTITUMORAL ECTEINASCIDIN DERIVATIVES



(VIa)



(VIb)

(57) Abstract: Compounds having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb) and compounds in which the $-NH_2$ or -OH of the 1,4 bridge is derivatised are disclosed. Such compounds are useful in the treatment of tumours.

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ANTITUMORAL ECTEINASCIDIN DERIVATIVES

The present invention relates to antitumoral ecteinascidin derivatives.

BACKGROUND OF THE INVENTION

The ecteinascidins are exceedingly potent antitumour agents isolated from the marine tunicate *Ecteinascidia turbinata*. Several ecteinascidins have been reported previously in the patent and scientific literature.

U.S. Patent N° 5,256,663 describes pharmaceutical compositions comprising matter extracted from the tropical marine invertebrate, *Ecteinascidia turbinata*, and designated therein as ecteinascidins, and the use of such compositions as antibacterial, anti-viral, and/or antitumour agents in mammals.

U.S. Patent N° 5,089,273 describes novel compositions of matter extracted from the tropical marine invertebrate, *Ecteinascidia turbinata*, and designated therein as ecteinascidins 729, 743, 745, 759A, 759B and 770. These compounds are useful as antibacterial and / or antitumour agents in mammals.

U.S. Patent N° 5,478,932 describes ecteinascidins isolated from the Caribbean tunicate *Ecteinascidia turbinata*, which provide *in vivo* protection against P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts.

U.S. Patent N° 5,654,426 describes several ecteinascidins isolated from the Caribbean tunicate *Ecteinascidia turbinata*, which provide in vivo protection against

P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts.

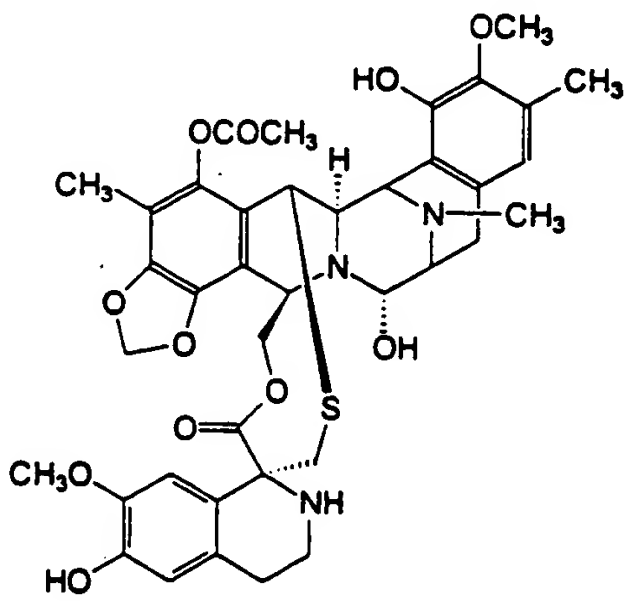
U.S. Patent N°. 5,721,362 describes a synthetic process for the formation of ecteinascidin compounds and related structures.

WO 00/69862, from which the present application claims priority, describes the synthesis of ecteinascidin compounds from cyanosafracin B.

The interested reader is also referred to: Corey, E.J., J. Am. Chem. Soc., 1996, 118 pp. 9202-9203; Rinehart, et al., Journal of National Products, 1990, "Bioactive Compounds from Aquatic and Terrestrial Sources", vol. 53, pp. 771-792; Rinehart et al., Pure and Appl. Chem., 1990, "Biologically active natural products", vol 62, pp. 1277-1280; Rinehart, et al., J. Org. Chem., 1990, "Ecteinascidins 729, 743, 745, 759A, 759B, and 770: Potent Antitumour Agents from the Caribbean Tunicate *Ecteinascidia turbinata*", vol. 55, pp. 4512-4515; Wright et al., J. Org. Chem., 1990, "Antitumour Tetrahydroisoquinoline Alkaloids from the Colonial Ascidian *Ecteinascidia turbinata*", vol. 55, pp. 4508-4512; Sakai et al., Proc. Natl. Acad. Sci. USA 1992, "Additional antitumour ecteinascidins from a Caribbean tunicate: Crystal structures and activities *in vivo*", vol. 89, 11456-11460; Science 1994, "Chemical Prospectors Scour the Seas for Promising Drugs", vol. 266,pp. 1324; Koenig, K.E., "Asymmetric Synthesis", ed. Morrison, Academic Press, Inc., Orlando, FL, vol. 5, 1985,p. 71; Barton, et al., J. Chem Soc. Perkin Trans., 1, 1982, "Synthesis and Properties of a Series of Sterically Hindered Guanidine Bases", pp. 2085; Fukuyama et al., J. Am Chem. Soc., 1982, "Stereocontrolled Total Synthesis of (+) – Saframycin B", vol. 104,pp. 4957; Fukuyama et al., J. Am Chem Soc., 1990, "Total Synthesis of (+) – Saframycin A", vol. 112, p. 3712; Saito, et al., J. Org. Chem., 1989, "Synthesis of Saframycins. Preparation of a Key Tricyclic Lactam Intermediate to Saframycin A", vol. 54, 5391; Still, et al., J. Org. Chem., 1978, "Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution", vol. 43, p. 2923; Kofron, W.G.; Baclawski, L.M., J. Org. Chem., 1976, vol. 41, 1879; Guan et al., J. Biomolec. Struc. & Dynam., vol. 10 pp. 793-817 (1993); Shamma et al., "Carbon-

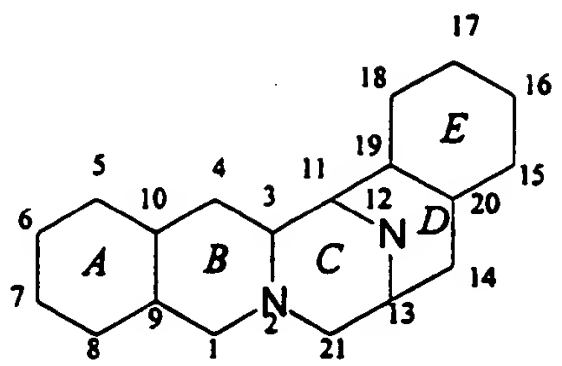
13 NMR Shift Assignments of Amines and Alkaloids", p. 206 (1979); Lown et al., Biochemistry, 21, 419-428 (1982); Zmijewski et al., Chem. Biol. Interactions, 52, 361-375 (1985); Ito, CRC CRIT. Rev. Anal. Chem., 17, 65-143 (1986); Rinehart et al., "Topics in Pharmaceutical Sciences 1989" pp. 613-626, D. D. Breimer, D.J. A. Cromwelin, K.K. Midha, Eds., Amsterdam Medical Press B.V., Noordwijk, The Netherlands (1989); Rinehart et al., "Biological Mass Spectrometry," 233-258 eds. Burlingame et al., Elsevier Amsterdam (1990); Guan et al., Jour. Biomolec. Struct. & Dynam., vol. 10 pp. 793-817 (1993); Nakagawa et al., J. Amer. Chem. Soc., 111: 2721-2722 (1989); Lichter et al., "Food and Drugs from the Sea Proceedings" (1972), Marine Technology Society, Washington, D.C.1973, 117-127; Sakai et al., J. Amer. Chem. Soc. 1996, 118, 9017; García-Rocha et al., Brit. J. Cancer, 1996, 73: 875-883; and Pommier et al., Biochemistry, 1996, 35: 13303-13309; Rinehart, K.L., *Med. Res. Rev.*, 2000, 20, 1-27 and I. Manzanares et al, *Org. Lett.*, 2000, 2(16), 2545-2548.

The most promising ecteinascidin is ecteinascidin 743, which is undergoing clinical trials for treatment of cancers. Et 743 has a complex tris(tetrahydroisoquinolinephenol) structure of the following formula (I):

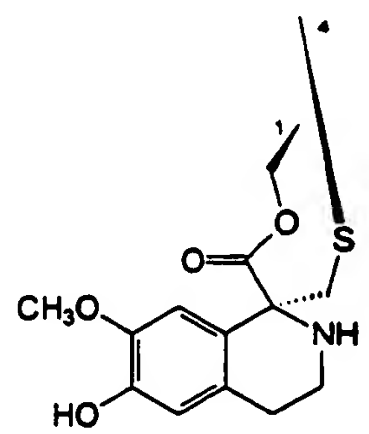


It is currently prepared by isolation from extracts of the marine tunicate *Ecteinascidin turbinata*. The yield is low, and alternative preparative processes have been sought.

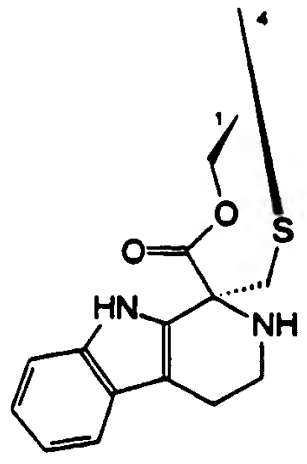
The ecteinascidins include a fused system of five rings (*A*) to (*E*) as shown in the following structure of formula (XIV):



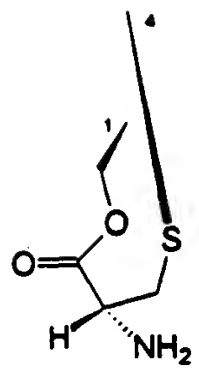
In ecteinascidin 743, the 1,4 bridge has the structure of formula (IV):



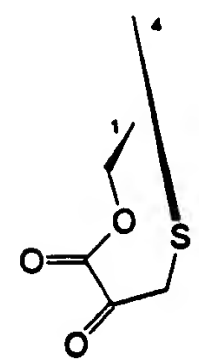
Other known ecteinascidins include compounds with a different bridged cyclic ring system, such as occurs in ecteinascidin 722 and 736, where the bridge has the structure of formula (V):



ecteinascidins 583 and 597, where the bridge has the structure of formula (VI):



and ecteinascidin 594 and 596, where the bridge has the structure of formula (VII):



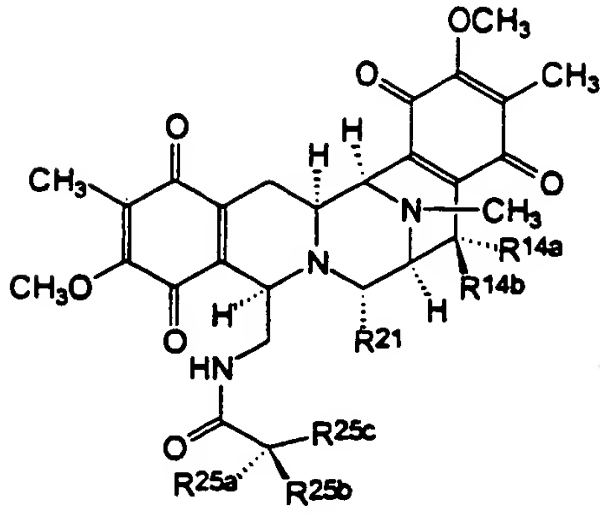
The complete structure for these and related compounds is given in J. Am. Chem. Soc. (1996) 118, 9017-9023.

Further compounds are known with the fused five ring system. In general, they lack the bridged cyclic ring system which is present in the ecteinascidins. They include the bis(tetrahydroisoquinolinequinone) antitumor-antimicrobial antibiotics safracins and saframycins, and the marine natural products renieramicins and xestomycin isolated from cultured microbes or sponges. They all have a common dimeric tetrahydroisoquinoline carbon framework. These compounds can be classified into four types, types I to IV, with respect to the oxidation pattern of the aromatic rings.

Type I, dimeric isoquinolinequinones, is a system of formula (VIII) most commonly occuring in this class of compounds, see the following table I.

Table I

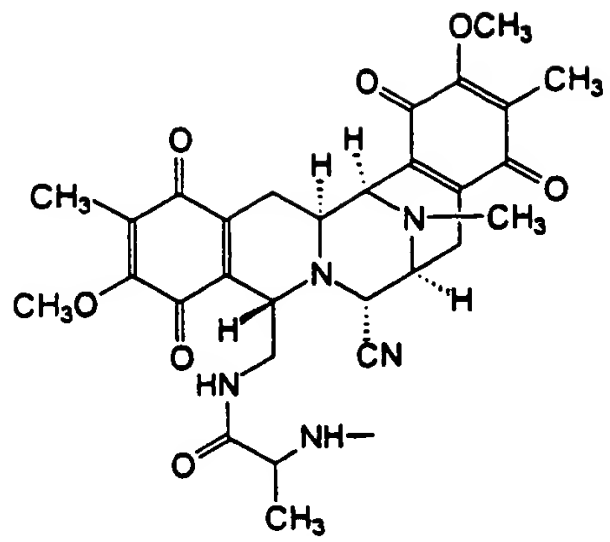
Structure of Type I Saframycin Antibiotics



	Substituents					
Compound	R^{14a}	R^{14b}	R^{21}	R^{25a}	R^{25b}	R^{25c}
saframycin A	H	H	CN	O	O	CH_3
saframycin B	H	H	H	O	O	CH_3
saframycin C	H	OCH_3	H	O	O	CH_3
saframycin G	H	OH	CN	O	O	CH_3
saframycin H	H	H	CN	OH	CH_2COCH_3	CH_3
saframycin S	H	H	OH	O	O	CH_3
saframycin Y_3	H	H	CN	NH_2	H	CH_3
saframycin Yd_1	H	H	CN	NH_2	H	C_2H_5
saframycin Ad_1	H	H	CN	O	O	C_2H_5
saframycin Yd_2	H	H	CN	NH_2	H	H
saframycin Y_{2b}	H	Q^b	CN	NH_2	H	CH_3
saframycin Y_{2b-d}	H	Q^b	CN	NH_2	H	C_2H_5
saframycin AH_2	H	H	CN	H^a	OH^a	CH_3
saframycin AH_2Ac	H	H	CN	H	OAc	CH_3
saframycin AH_1	H	H	CN	OH^a	H^a	CH_3
saframycin AH_1Ac	H	H	CN	OAc	H	CH_3
saframycin AR_3	H	H	H	H	OH	CH_3

[a] assignments are interchangeable.

[b] where the group Q is of formula (IX):

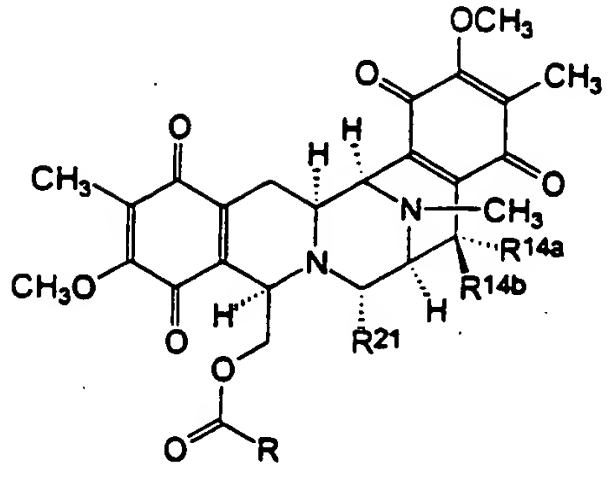


Type I aromatic rings are seen in saframycins A, B and C; G and H; and S isolated from *Streptomyces lavendulae* as minor components. A cyano derivative of saframycin A, called cyanoquinonamine, is known from Japanese Kokai JP-A2 59/225189 and 60/084288. Saframycins Y_3, Yd_1, Ad_1 and Yd_2 were produced by *S. lavendulae* by directed biosynthesis, with appropriate supplementation of the culture medium. Saframycins Y_{2b} and Y_{2b-d} dimers formed by linking the nitrogen on the C-25 of one unit to the C-14 of the other,have also been produced in supplemented culture medium of *S. lavendulae*. Saframycins AR_1 (=AH_2), a microbial reduction product of saframycin A at C-25 produced by *Rhodococcus amidophilus*, is also prepared by nonstereoselective chemical reduction of saframycin A by sodium borohydride as a 1:1 mixture of epimers followed by chromatographic separation (the other isomer AH_1 is less polar). The further reduction product saframycin AR_3, 21-decyano-25-dihydro-saframycin A, (= 25-dihydrosaframycin B) was produced by the same microbial conversion. Another type of microbial conversion of saframycin A using a *Nocardia* species produced saframycin B and further reduction by a *Mycobacterium* species produced saframycin AH^1Ac. The 25-O-acetates of saframycin AH_2 and AH_1 have also been prepared chemically for biological studies.

Type I compounds of formula (X) have also been isolated from marines sponges, see Table II.

Table II

Structures of Type I Compounds from Marine Sponges



	Substituents			
	R^{14a}	R^{14b}	R^{21}	R
renieramycin A	OH	H	H	$-C(CH_3)=CH-CH_3$
renieramycin B	OC_2H_5	H	H	$-C(CH_3)=CH-CH_3$
renieramycin C	OH	O	O	$-C(CH_3)=CH-CH_3$
renieramycin D	OC_2H_5	O	O	$-C(CH_3)=CH-CH_3$
renieramycin E	H	H	OH	$-C(CH_3)=CH-CH_3$
renieramycin F	OCH_3	H	OH	$-C(CH_3)=CH-CH_3$
xestomycin	OCH_3	H	H	$-CH_3$

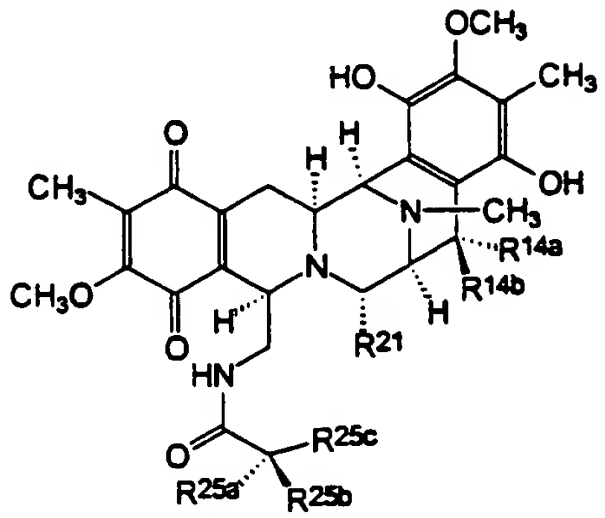
Renieramycins A-D were isolated from the antimicrobial extract of a sponge, a *Reniera* species collected in Mexico, along with the biogenetically related monomeric isoquinolines renierone and related compounds. The structure of renieramycin A was initially assigned with inverted stereochemistry at C-3, C-11, and C-13. However, careful examination of the ^1H NMR data for new, related compounds renieramycins E and F, isolated from the same sponge collected in Palau, revealed that the ring junction of renieramycins was identical to that of saframycins. This result led to the conclusion that the formerly assigned stereochemistry of renieramycins A to D must be the same as that of saframycins.

Xestomycin was found in a sponge, a *Xestospongia* species collected from Sri Lankan waters.

Type II compounds of formula (XI) with a reduced hydroquinone ring include saframycins D and F, isolated from *S. lavendulae*, and saframycins Mx-1 and Mx-2, isolated from *Myxococcus xanthus*. See table III.

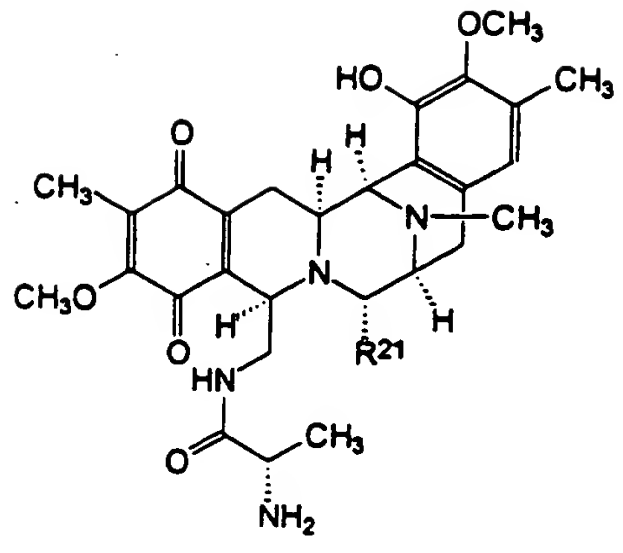
Table III

Type II Compounds



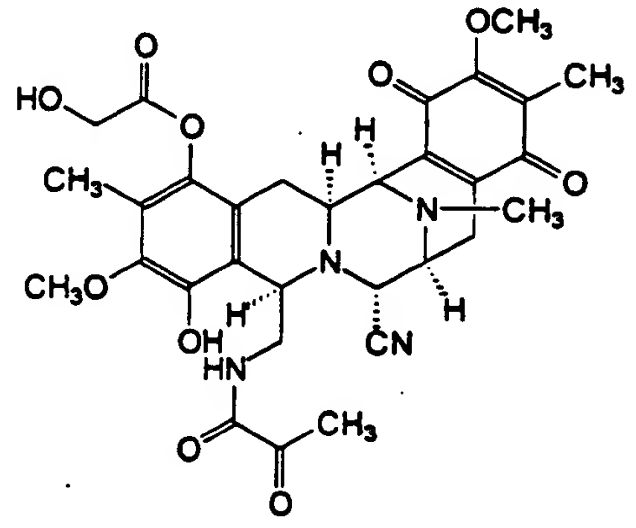
	Substituents					
Compound	R^{14a}	R^{14b}	R^{21}	R^{25a}	R^{25b}	R^{25c}
saframycin D	O	O	H	O	O	CH_3
saframycin F	O	O	CN	O	O	CH_3
saframycin Mx-1	H	OCH_3	OH	H	CH_3	NH_2
saframycin Mx-2	H	OCH_3	H	H	CH_3	NH_2

The type III skeleton is found in the antibiotics safracins A and B, isolated from cultured *Pseudomonas fluorescens*. These antibiotics of formula (XII) consist of a tetrahydroisoquinoline-quinone subunit and a tetrahydroisoquinolinephenol subunit.

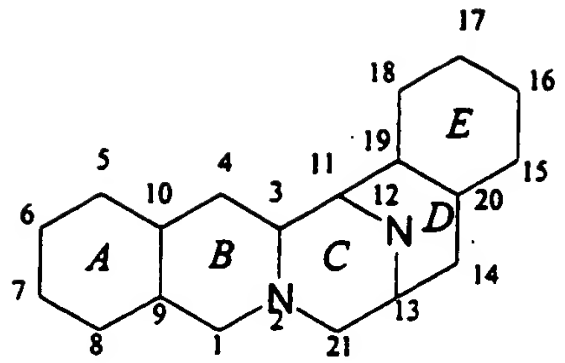


Where R^{21} is –H in safracin A and is –OH in safracin B.

Saframycin R, the only compound classified as the Type IV skeleton, was also isolated from *S. lavendulae*. This compound of formula (XIII), consisting of a hydroquinone ring with a glycolic ester side chain on one of the phenolic oxygens, is conceivably a pro-drug of saframycin A because of its moderate toxicity.



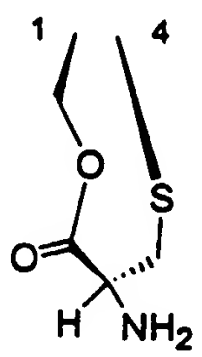
These known compounds include the fused system of five rings of the formula (XIV):



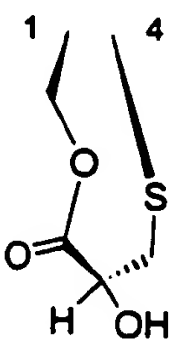
In this text, we refer to this ring structure as the fused ecteinascidin five ring system, though it will be appreciated that the rings *A* and *E* are phenolic in the ecteinascidins and some other compounds, while in other compounds, notably the saframycins, the rings *A* and *E* are quinolic. In the compounds, the rings *B* and *D* are tetrahydro, while ring *C* is perhydro.

SUMMARY OF THE INVENTION

The present invention provides compounds having the fused ecteinascidin five ring system and related to ecteinascidins 583 and 597. In ecteinascidins 583 and 597 the 1,4 bridge has the structure of formula (VIa):



VIa



VIb

Certain compounds of this invention have the fused five ring system of ecteinascidins and the bridge structure of formula (VIa), with the $-NH_2$ optionally derivatised. These compounds can be acylated on the $-CHNH_2-$ group present in the formula (VI). Other derivative compounds of this invention comprise those where this $-CHNH_2-$ group is replaced by a group $-CHNHX_1$ or $-C(X_2)_2-$ where X_1 or X_2 are as

defined. The remaining substituents on the fused ecteinascidin five ring system can be the same as those on natural compounds, particularly natural ecteinascidins, or different.

Other compounds of this invention have the fused five ring system of ecteinascidins and the bridge structure of formula (VIb) in which the $-NH_2$ group on the bridge has been replaced with an -OH group which may be optionally derivatised. These compounds can be acylated on the -CHOH- group present in the formula (VIb). Other derivative compounds of this invention comprise those where this –CHOH- group is replaced by a group - $CHOX_1$ or $-C(X_2)_2$- where X_1 or X_2 are as defined. The remaining substituents on the fused ecteinascidin five ring system can be the same as those on natural compounds, particularly natural ecteinascidins, or different.

In the compounds of this invention, the stereochemistry of the bridgehead carbon atom bearing the –OH or $-NH_2$ group (or substituted derivatives thereof) can be the same as that of the natural compounds, particularly natural ecteinascidins, or different.

In the compounds of this invention, the fused system of five rings (*A*) to (*E*) of formula (XIV) can be as in the ecteinascidins, or may be as in other related compounds. Thus the rings *A* and *E* can be phenolic or quinolic; the rings *B* and *D* are tetrahydro, and ring *C* is perhydro.

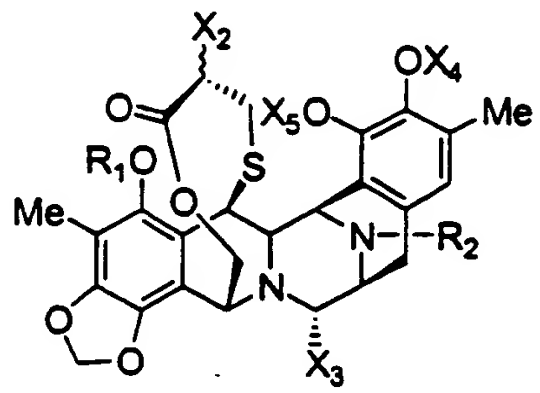
Compounds of this invention exhibit antitumor activity, and the invention provides pharamaceutical compositions of the compounds, along with methods for preparing the compositions and methods of treatment using the compounds or compositions.

The invention also provides new hemisynthetic and synthetic routes to the compounds of this invention.

PREFERRED EMBODIMENTS

The fused system of five rings (*A*) to (*E*) of formula (XIV) is preferably as in the ecteinascidins, and preferably substituted in positions other than 1,4 with naturally occurring substituents.

In one aspect, the present invention provides new compounds of the formula:



wherein:

the substituent groups defined by R_1, R_2 are each independently selected of H, C(=O)R′, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl; each of the R′ groups is independently selected from the group consisting of H, OH, NO_2, NH_2, SH, CN, halogen, =O, C(=O)H, $C(=O)CH_3$, CO_2H, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl;

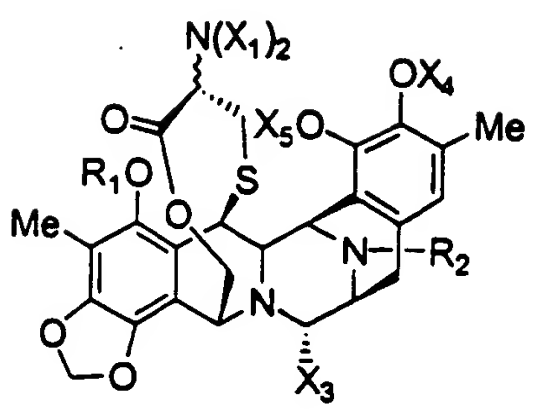
X_2 is OX_1 or $N(X_1)_2$ wherein the or each X_1 is H, C(=O)R′, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl, or two X_1 groups may together form a cyclic substituent on the nitrogen atom;

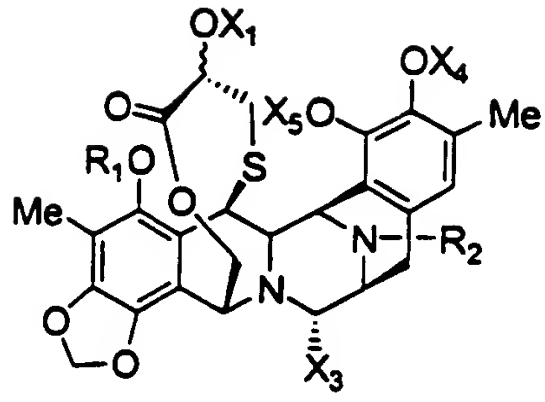
X_3 is selected of OR_1, CN, (=O), or H;

X_4 is –H or C_1-C_{18} alkyl; and

X_5 is selected of H, OH, or –OR_1 (wherein OR_1 is as defined above).

In a related aspect, the invention provides compounds of formula:





wherein the substituent groups defined by R_1, R_2, X_3, X_4 and X_5 are as defined; and X_1 is independently selected of H, C(=O)R′, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl, or two X_1 groups may together form a cyclic susbstituent on the nitrogen atom.

Alkyl groups preferably have from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms. Methyl, ethyl and propyl including isopropyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members. The alkyl groups may be straight chain or branched chain.

Preferred alkenyl and alkynyl groups in the compounds of the present invention have one or more unsaturated linkages and from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more preferably 2 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refer to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred.

Preferred alkoxy groups in the compounds of the present invention include groups having one or more oxygen linkages and from 1 to about 12 carbon atoms, more preferably from

1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms.

Preferred alkylthio groups in the compounds of the present invention have one or more thioether linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylthio groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfinyl groups in the compounds of the present invention include those groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfinyl groups having 1, 2 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfonyl groups in the compounds of the present invention include those groups having one or more sulfonyl (SO2) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred aminoalkyl groups include those groups having one or more primary, secondary and/or tertiary amine groups, and from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. Secondary and tertiary amine groups are generally more preferred than primary amine moieties.

Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl and benzothiazolyl. Suitable heteroalicyclic groups in the compounds of the present invention

contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl groups.

Suitable carbocyclic aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain separate and / or fused aryl groups. Typical carbocyclic aryl groups contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred carbocyclic aryl groups include phenyl including substituted phenyl such as 2-substituted phenyl, 3-substituted phenyl, 2, 3-substituted phenyl, 2,5-substituted phenyl, 2,3,5-substituted and 2,4,5-substituted phenyl, including where one or more of the phenyl substituents is an electron-withdrawing group such as halogen, cyano, nitro, alkanoyl, sulfinyl, sulfonyl and the like; naphthyl including 1-naphthyl and 2-naphthyl; biphenyl; phenanthryl; and anthracyl.

Substituent groups defined by R_1, R_2, X_1, X_4 and X_5 are each independently selected from the group consisting of H, OH, OR′, SH, SR′, SOR′, SO_2R', NO_2, NH_2, NHR′, $N(R')_2$, NHC(O)R′, CN, halogen, =O, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaromatic.

References herein to substituted R′ groups in the compounds of the present invention refer to the specified moiety that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a fluoro, chloro, bromo and iodo: cyano; hydroxyl; nitro; azido; alkanoyl such as a C1-6 alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more

thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocylic aryl having 6 or more carbons, particularly phenyl (e.g., R being a substituted or unsubstituted biphenyl moiety); and aralkyl such as benzyl.

R_1 is peferably C(=O)R′, where R′ is suitably H or substituted or unsubstituted alkyl, more preferably acetyl.

R_2 is preferably H or methyl, more preferably methyl.

Typically one of X_1 or X_2 is often hydrogen. X_2, or where permitted X_1 is preferably H; -NHCOalkyl, particularly where the alkyl has up to 16 carbon atoms, such as 1, 4, 7, 15 carbon atoms and may be halosubstituted optionally perhalosubstituted; -NHalkylCOOH particularly where the alkyl has up to 4 carbon atoms; protected $-NHCOCH(NH_2)CH_2SH$ where the NH_2 and/or the SH are protected; -NHbiotin; -NHaryl; $-NH(aa)_y$ where aa is an amino acid acyl and y is suitably 1, 2 or 3 and wherein any NH_2 is optionally derivatised or protected, as with an amide terminal group or a Boc group; phthalimido formed $-NX_2-$; alkyl preferably having 1 to 4 carbon atoms; arylalkenyl, especially cinnamoyl which may be substituted as with 3-trifluoromethyl;

Preferred examples of the group X_2 include NHAc, $NHCO(CH_2)_2COOH$, NHCOCH(NHAlloc)CH_2SFm, $NHCO(CH_2)_{14}CH_3$, NHTFA, $NHCO(CH_2)_2CH_3$, $NHCOCH_2CH(CH_3)_2$, $NHCO(CH_2)_6CH_3$, NHBiotin, NHBz, NHCOCinn, NHCO-(*p*-F_3C)-Cinn, NHCOVal-NH_2, NHCOVal-*N*-Ac, NHCOVal-*N*-COCinn, NHCOVal-Ala-NH_2, NHCOVal-Ala-*N*-Ac, NHCOAla-NH_2, OH, OAc, NHAc, $NHCO(CH_2)_2COOH$, NHCOCH(NHAlloc)CH_2SFm, NHCOCH(NH_2)CH_2SFm, NPht, NH-(*m*-CO_2Me)-Bz, $NHCO(CH_2)_{14}CH_3$, NMe_2, NHTFA, $NHCO(CH_2)_2CH_3$, $NHCOCH_2CH(CH_3)_2$,

$NHCO(CH_2)_6CH_3$, NHAlloc, NHTroc, NHBiotin, NHBz, NHCOCinn, NHCO-(*p*-F_3C)-Cinn, $NHCOVal\text{-}NH_2$, NHCOVal-*N*-Ac, NHCOVal-*N*-COCinn, $NHCOVal\text{-}Ala\text{-}NH_2$, NHCOVal-Ala-*N*-Ac, NHCOVal-Ala-*N*-COCinn, $NHCOAla\text{-}NH_2$, NHCOAla-*N*-Ac, NHCOAla-*N*-COCinn, OH, OAc, NHAc, $NHCO(CH_2)_2COOH$, $NHCOCH(NHAlloc)CH_2SFm$, Npht, along with similar groups where the number of carbon atoms is varied or the amino acid is changed or another change of this kind is made to give a similar group.

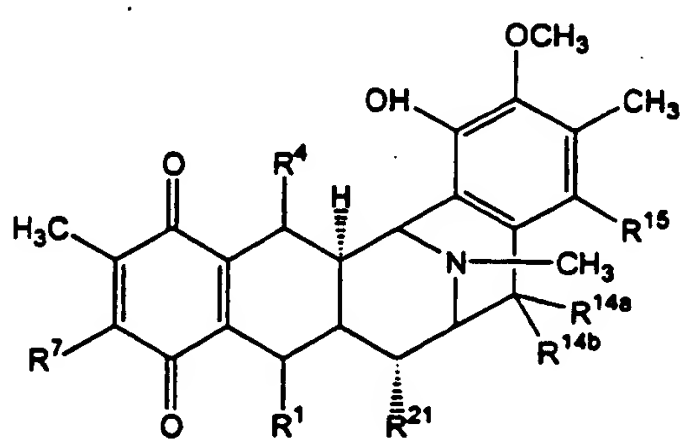
Other preferred examples of the group X_2 include OH, OAc, $OCOCF_3$, $OCOCH_2CH_2CH_3$, $OCO(CH_2)_6CH_3$, $OCO(CH_2)_{14}CH_3$, OCOCH=CHPh, OSO_2CH_3 along with similar groups where the number of carbon atoms is varied or different substituent groups are introduced or another change of this kind is made to give a similar group.

X_3 is preferably OH or CN.

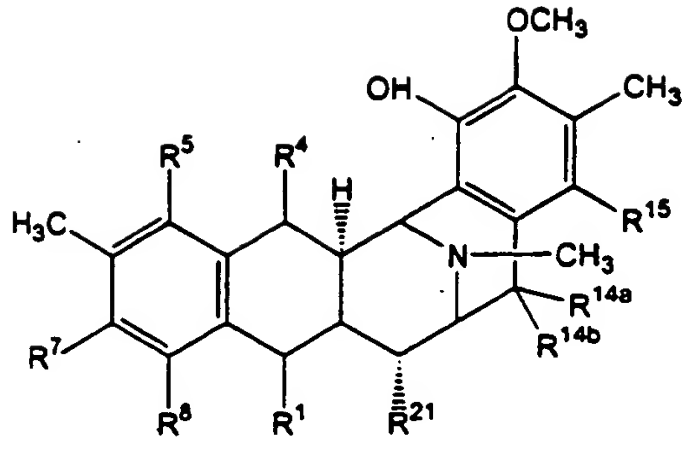
X_4 is H or Me, preferably Me.

X_5 is H or $C_{1\text{-}18}$ alkyl, preferably H.

In a further, more general aspect of this invention, the compounds are typically of the formula (XVIIa):

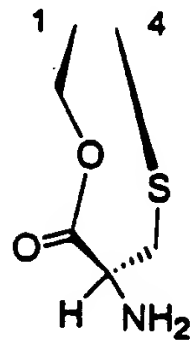


or formula (XVIIb):

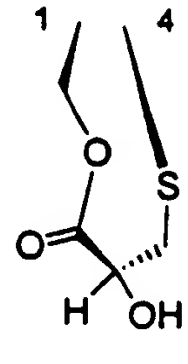


where

R^1 and R^4 together form a group of formula (VIa) or (VIb):



VIa



VIb

R^5 is -H or -OH;

R^7 is $-OCH_3$ and R^8 is -OH or R^7 and R^8 together form a group $-O-CH_2-O-$;

R^{14a} and R^{14b} are both -H or one is -H and the other is -OH, $-OCH_3$ or $-OCH_2CH_3$, or R^{14a} and R^{14b} together form a keto group; and

R^{15} is -H or -OH;

R^{21} is -H, -OH or -CN;

and derivatives including acyl derivatives thereof especially where R^5 is acetyloxy or other acyloxy group of up to 4 carbon atoms, and including derivatives where the group $-NCH_3-$ at the 12-position is replaced by -NH- or $-NCH_2CH_3-$, and derivatives where the $-NH_2$ group in the compound of formula (VIa) and the – OH group in the compound of formula (VIb) are optionally derivatised.

The group R_1 with R_4 can be acylated on the $-CHNH_2-$ or -CHOH – group present in the formulae (VIa and VIb). Other derivative compounds of this invention comprise those where the $-CHNH_2$ group of VIa is replaced by a group $-CHNHX_1$ or –

$C(X_2)_2$- or where the –CHOH group of VIb is replaced by $CHOX_1$ or $-C(X_2)_2-$ where X_1 or X_2 are as defined.

Preferred compounds are of the formula (XVIIb).

Furthermore, in preferred compounds of this invention, R^7 and R^8 together form a group $-O-CH_2-O-$.

The acyl derivatives can be N-acyl or N-thioacyl derivatives thereof, as well as cyclic amides. The acyl groups can illustratively be alkanoyl, haloalkanoyl, arylalkanoyl, alkenyl, heterocyclylacyl, aroyl, arylaroyl, haloaroyl, nitroaroyl, or other acyl groups. The acyl groups can be of formula $-CO-R^a$, where R^a can be various groups such as alkyl, alkoxy, alkylene, arylalkyl, arylalkylene, amino acid acyl, or heterocyclyl, each optionally substituted with halo, cyano, nitro, carboxyalkyl, alkoxy, aryl, aryloxy, heterocyclyl, heterocycyloxy, alkyl, amino or substituted amino. Other acylating agents include isothiocyanates, such as aryl isothiocyanates, notably phenyl isocyanate. The alkyl, alkoxy or alkylene groups of R^a suitably have 1 to 6 or 12 carbon atoms, and can be linear, branched or cyclic. Aryl groups are typically phenyl, biphenyl or naphthyl. Hetercyclyl groups can be aromatic or partially or completely unsaturated and suitably have 4 to 8 ring atoms, more preferably 5 or 6 ring atoms, with one or more heteroatoms selected from nitrogen, sulphur and oxygen.

Without being exhaustive, typical R^a groups include alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, arylalkylene, haloalkylarylakylene, acyl, haloacyl, arlyalkyl, alkenyl and amino acid. For example, R^a-CO- can be acetyl, trifluoroacetyl, 2,2,2-trichloroethoxycarbonyl, isovalerylcarbonyl, trans-3-(trifluoromethyl)cinnamoylcarbonyl, heptafluorobutyrylcarbonyl, decanoylcarbonyl, trans-cinnamoylcarbonyl, butyrylcarbonyl, 3-chloropropyonylcarbonyl, cinnamoylcarbonyl, 4-methylcinnamoylcarbonyl, hydrocinnamoylcarbonyl, or trans-hexenoylcarbonyl, or alanyl, arginyl, aspartyl, asparagyl, cystyl, glutamyl, glutaminyl, glycyl, histidyl, hydroxyprolyl., isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, prolyl, seryl, threonyl,

thyronyl, tryptophyl, tyrosyl, valyl, as well as other less common amino acid acyl groups, as well as phthalimido and other cyclic amides. Other examples may be found among the listed protecting groups.

Compounds wherein -CO-R^a is derived from an amino acid and include an amino group can themselves form acyl derivatives. Suitable N-acyl commands include dipeptides which in turn can form N-acyl derivatives.

Preferably R^{14a} and R^{14b} are hydrogen. Preferably R^{15} is hydrogen. The O-acyl derivatives are suitably aliphatic O-acyl derivatives, especially acyl derivatives of 1 to 4 carbon atoms, and typically an O-acetyl group, notably at the 5-position.

Suitable protecting groups for phenols and hydroxy groups include ethers and esters, such as alkyl, alkoxyalkyl, aryloxyalkyl, alkoxyalkoxyalkyl, alkylsilylalkoxyalkyl, alkylthioalkyl, arylthioalkyl, azidoalkyl, cyanoalkyl, chloroalkyl, heterocyclic, arylacyl, haloarylacyl, cycloalkylalkyl, alkenyl, cycloalkyl, alyklarylalkyl, alkoxyarylalkyl, nitroarylalkyl, haloarylalkyl, alkylaminocarbonylarylalkyl, alkylsulfinylarylalkyl, alkylsilyl and other ethers, and arylacyl, aryl alkyl carbonate, aliphatic carbonate, alkylsulfinylarlyalkyl carbonate, alkyl carbonate, aryl haloalkyl carbonate, aryl alkenyl carbonate, aryl carbamate, alkyl phosphinyl, alkylphosphinothioyl, aryl phosphinothioyl, aryl alkyl sulphonate and other esters. Such groups may optionally be substituted with the previously mentioned groups in R^1.

Suitable protecting groups for amines include carbamates, amides, and other protecting groups, such as alkyl, arylalkyl, sulpho- or halo- arylalkyl, haloalkyl, alkylsilylalkyl, arylalkyl, cycloalkylalkyl, alkylarylalkyl, heterocyclylalkyl, nitroarylalkyl, acylaminoalkyl, nitroaryldithioarylalkyl, dicycloalkylcarboxamidoalkyl, cycloalkyl, alkenyl, arylalkenyl, nitroarylalkenyl, heterocyclylalkenyl, heterocyclyl, hydroxyheterocyclyl, alkyldithio, alkoxy- or halo- or alkylsulphinyl arylalkyl, hetercyclylacyl, and other carbamates, and alkanoyl, haloalkanoyl, arylalkanoyl, alkenoyl, heterocyclylacyl, aroyl, arylaroyl, haloaroyl, nitroaroyl, and other amides, as

well as alkyl, alkenyl, alkylsilylalkoxyalkyl, alkoxyalkyl, cyanoalkyl, heterocyclyl, alkoxyarylalkyl, cycloalkyl, nitroaryl, arylalkyl, alkoxy- or hydroxy- arylalkyl, and many other groups. Such groups may optionally be substituted with the previously mentioned groups in R^1.

Examples of such protecting groups are given in the following tables.

protection for -OH group

ethers	abbreviation
methyl	
methoxymethyl	MOM
benzyloxymethyl	BOM
methoxyethoxymethyl	MEM
2-(trimethylsilyl)ethoxymethyl	SEM
methylthiomethyl	MTM
phenylthiomethyl	PTM
azidomethyl	
cyanomethyl	
2,2-dichloro-1,1-difluoroethyl	
2-chloroethyl	
2-bromoethyl	
tetrahydropyranyl	THP
1-ethoxyethyl	EE
phenacyl	
4-bromophenacyl	
cyclopropylmethyl	
allyl	
propargyl	
isopropyl	

cyclohexyl	
t-butyl	
benzyl	
2,6-dimethylbenzyl	
4-methoxybenzyl	MPM or PMB
o-nitrobenzyl	
2,6-dichlorobenzyl	
3,4-dichlorobenzyl	
4-(dimethylamino)carbonylbenzyl	
4-methylsuflinylbenzyl	Msib
9-anthrylmethyl	
4-picolyl	
heptafluoro-*p*-tolyl	
tetrafluoro-4-pyridyl	
trimethylsilyl	TMS
t-butyldimethylsilyl	TBDMS
t-butyldiphenylsilyl	TBDPS
triisopropylsilyl	TIPS

esters	
aryl formate	
aryl acetate	
aryl levulinate	
aryl pivaloate	ArOPv
aryl benzoate	
aryl 9-fluorocarboxylate	
aryl methyl carbonate	
1-adamantyl carbonate	
t-butyl carbonate	BOC-OAr
4-methylsulfinylbenzyl carbonate	Msz-Oar
2,4-dimethylpent-3-yl carbonate	Doc-Oar
aryl 2,2,2-trichloroethyl carbonate	
aryl vinyl carbonate	
aryl benzyl carbonate	
aryl carbamate	
dimethylphosphinyl	Dmp-OAr
dimethylphosphinothioyl	Mpt-OAr
diphenylphosphinothioyl	Dpt-Oar
aryl methanesulfonate	
aryl toluenesulfonate	
aryl 2-formylbenzenesulfonate	

protection for the -NH_2 group

carbamates	abbreviation
methyl	
ethyl	
9-fluorenylmethyl	Fmoc
9-(2-sulfo)fluroenylmethyl	
9-(2,7-dibromo)fluorenylmethyl	
17-tetrabenzo[*a,c,g,i*]fluorenylmethyl	Tbfmoc
2-chloro-3-indenylmethyl	Climoc
benz[*f*]inden-3-ylmethyl	Bimoc
2,7-di-*t*-butyl[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl	DBD-Tmoc
2,2,2-trichloroethyl	Troc
2-trimethylsilylethyl	Teoc
2-phenylethyl	hZ
1-(1-adamantyl)-1-methylethyl	Adpoc
2-chlooethyl	
1,1-dimethyl-2-chloroethyl	
1,1-dimethyl-2-bromoethyl	
1,1-dimethyl-2,2-dibromoethyl	DB-*t*-BOC
1,1-dimethyl-2,2,2-trichloroethyl	TCBOC
1-methyl-1-(4-biphenyl)ethyl	Bpoc
1-(3,5-di-*t*-butylphenyl)-1-1-methylethyl	*t*-Burmeoc
2-(2'-and 4'-pyridyl)ethyl	Pyoc
2,2-bis(4'-nitrophenyl)ethyl	Bnpeoc
n-(2-pivaloylamino)-1,1-dimethylethyl	
2-[(2-nitrophenyl)dithio]-1-phenylethyl	NpSSPeoc

2-(*n*,*n*-dicyclohexylcarboxamido)ethyl	
t-butyl	BOC
1-adamantyl	1-Adoc
2-adamantyl	2-Adoc
vinyl	Voc
allyl	Aloc or Alloc
1-isopropylallyl	Ipaoc
cinnamyl	Coc
4-nitrocinnamyl	Noc
3-(3'-pyridyl)prop-2-enyl	Paloc
8-quinolyl	
n-hydroxypiperidinyl	
alkyldithio	
benzyl	Cbz or Z
p-methoxybenzyl	Moz
p-nitrobenzyl	PNZ
p-bromobenzyl	
p-chlorobenzyl	
2,4-dichlorobenzyl	
4-methylsulfinylbenzyl	Msz
9-anthrylmethyl	
diphenylmethyl	
phenothiazinyl-(10)-carbonyl	
n'-*p*-toluenesulfonylaminocarbonyl	
n'-phenylaminothiocarbonyl	

amides	
formamide	
acetamide	
chloroacetamide	
trifluoroacetamide	TFA
phenylacetamide	
3-phenylpropanamide	
pent-4-enamide	
picolinamide	
3-pyridylcarboxamide	
benzamide	
p-phenylbenzamide	
n-phthalimide	
n-tetrachlorophthalimide	TCP
4-nitro-*n*-phthalimide	
n-dithiasuccinimide	Dts
n-2,3-diphenylmaleimide	
n-2,5-dimethylpyrrole	
n-2,5-bis(triisopropylsiloxyl)pyrrole	BIPSOP
n-1,1,4,4-tetramethyldisiliazacyclopentante adduct	STABASE
1,1,3,3-tetramethyl-1,3-disilaisoindoline	BSB
special -NH protective groups	
n-methylamine	
n-*t*-butylamine	
n-allylamine	
n-[2-trimethylsilyl)ethoxy]methylamine	SEM

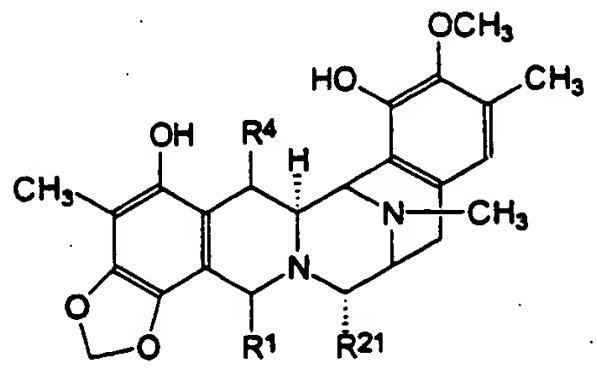
n-3-acetoxypropylamine	
n-cyanomethylamine	
n-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl)amine	
n-2,4-dimethoxybenzylamine	Dmb
2-azanorbornenes	
n-2,4-dinitrophenylamine	
n-benzylamine	Bn
n-4-methoxybenzylamine	MPM
n-2,4-dimethoxybenzylamine	DMPM
n-2-hydroxybenzylamine	Hbn
n-(diphenylmethyl)amino	DPM
n-bis(4-methoxyphenyl)methylamine	
n-5-dibenzosuberylamine	DBS
n-triphenylmethylamine	Tr
n-[(4-methoxyphenyl)diphenylmethyl]amino	MMTr
n-9-phenylflurenylamine	Pf
n-ferrocenylmethylamine	Fcm
n-2-picolylamine *n'*-oxide	
n-1,1-dimethylthiomethyleneamine	
n-benzylideneamine	
n-*p*-methoxybenzylideneamine	
n-diphenylmethyleneamine	
n-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine	
n-nitroamine	
n-nitrosoamine	
diphenylphosphinamide	Dpp
dimethylthiophosphinamide	Mpt
diphenylthiophosphinamide	Ppt
dibenzyl phosphoramidate	
2-nitrobenzenesulfenamide	Nps
n-1-(2,2,2-trifluoro-1,1-diphenyl)ethylsufenamide	TDE

3-nitro-2-pyridinesulfenamide	Npys
p-toluenesulfonamide	Ts
benzenesulfonamide	

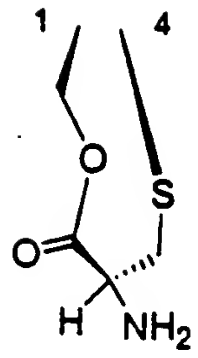
A preferred class of compounds of this invention include compunds of formula (XVIIb), where one or more, preferably all of the following conditions are met:

the amino group in the group of formula (VIa) is derivatised;
the hydroxy group in the group of formula (VIb) is derivatised;
R^5 is OR_1;
R^7 and R^8 together form a group $-O-CH_2-O-$;
R^{14a} and R^{14b} are both –H;
R^{15} is H; and/or
R^{21} is –OH or –CN.

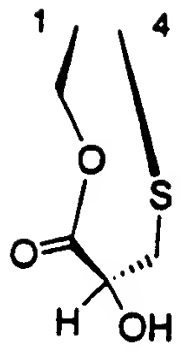
Particular ecteinascidin products of this invention include compounds of the formula (XVIII);



where R1 and R4 form a group of formula (VIa or VIb):



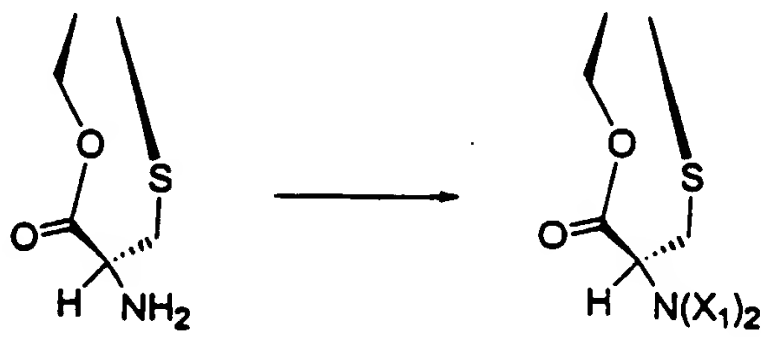
VIa



VIb

R^{21} is-H, -OH or –CN, more particularly –OH or –CN;
and acyl derivatives thereof, more particularly 5-acyl derivatives including the 5-acetyl derivative, and where the $-NH_2$ group in the structure of formula (VIa) and the –OH group in the structure of formula (VIb) are optionally derivatised.

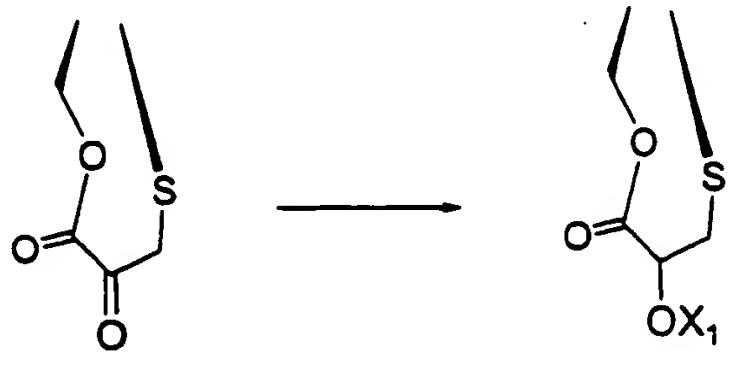
Compounds of the present invention notably with one of two group X_1 can be prepared synthetically from the intermediate compound (47) desribed in the U.S. Patent No 5,721,362, or a similar compound. Thus the present invention provides a process which involves derivatisation of the 1,4 bridge amino group, according to the following reaction scheme:



where X_1 is as defined, and other substituent groups on the molecule can be protected or derivatised as desired or appropriate.

Compounds of this invention notably with the groups X_2 being $-OX_2$ can be prepared from the intermediate compound (15) described in the U.S. Patent No 5,721,362

or a similar compound. Thus, the present invention provides a process which involves derivatisation of the 1,4 bridge amino group, according to the following reaction scheme:

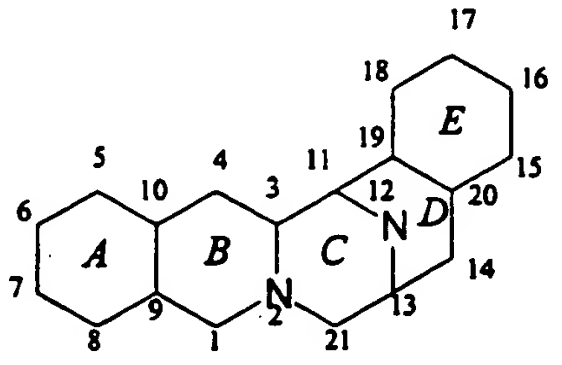


where X_1 is as defined, and other substituent groups on the molecule can be protected or derivatised as desired or appropriate. The reaction may proceed with formation of a substituent $-OX_1$ where X_1 is hydrogen, and then conversion to a compound where X_1 is another group.

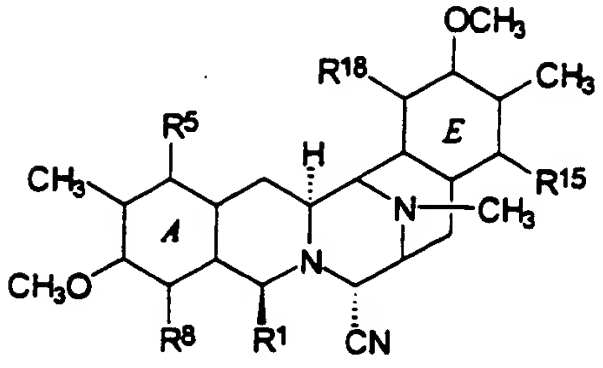
It will be apparent that compounds of this invention may also be prepared by modification of the synthetic steps employed in the U.S. Patent No 5,721,362. Thus, for instance, different reactive groups may be introduced at functional positions, for example at the 5- or 18- positions.

A more general route to compounds if this invention is provided, and was first disclosed in WO 00/69862, incorporated herein in full by reference and from which priority is claimed.

A typical process of that WO application concerns method for preparing a compound with a fused ring structure of formula (XIV):



which comprises one or more reactions starting from a 21-cyano compound of formula (XVI):



where:

R^1 is an amidomethylene group or an acyloxymethylene group;
R^5 and R^8 are independently chosen from –H, -OH or $-OCOCH_2OH$, or R^5 and R^8 are both keto and the ring *A* is a *p*-benzoquinone ring;
R^{14a} and R^{14b} are both –H or one is –H and the other is –OH, $-OCH_3$ or $-OCH_2CH_3$ or R^{14a} and R^{14b} together form a keto group; and
R^{15} and R^{18} are independently chosen from –H or –OH, or R^5 and R^8 are both keto and the ring *A* is a *p*-benzoquinone ring.

In particular, such a method can provide a route to the starting materials for the reactions of Schemes I and II, along with related compounds.

Antitumoural activities of these compounds include leukaemias, lung cancer, colon cancer, kidney cancer, prostate cancer, ovarian cancer, breast cancer, sarcomas and melanomas.

Another especially preferred embodiment of the present invention is pharmaceutical compositions useful as antitumour agents which contain as active

ingredient a compound or compounds of the invention, as well as the processes for their preparation.

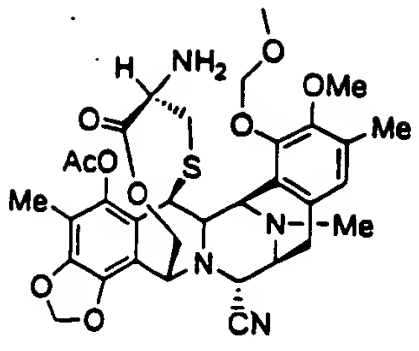
Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration.

Administration of the compounds or compositions of the present invention may be any suitable method, such as intravenous infusion, oral preparation, intraperitoneal and intravenous preparation.

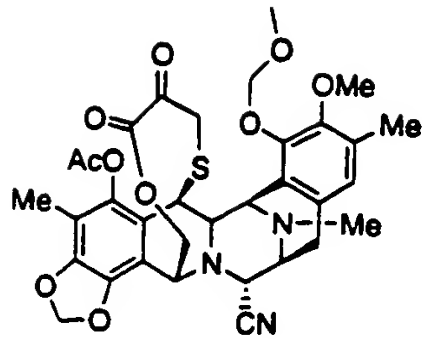
For the avoidance of doubt, the stereochemistries indicated in this patent specification are based on our understanding of the correct stereochemistry of the natural products. To the extent that an error is discovered in the assigned stereochemistry, then the appropriate correction needs to be made in the formulae given throughout in this patent specification. Furthermore, to the extent that the syntheses are capable of modification, this invention extends to stereoisomers.

DETAILED DESCRIPTION OF PREFERRED PROCESSES

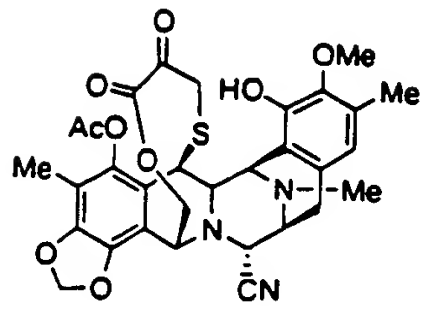
The compounds of the present invention can be synthetically prepared from the intermediate compounds 47 and 15 described in the U.S. Patent No 5,721,362, the compound 36 described in WO 00/69862 and from the secondary products (numbered here as 23 and 24) obtained in some deprotection steps using $AlCl_3$ of the compound 33 of WO 00/69862.



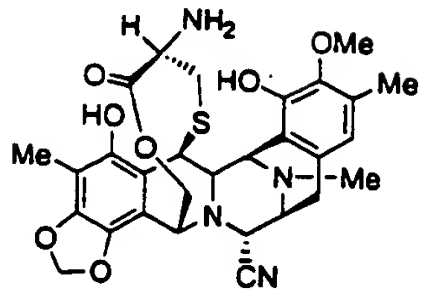
47 (1)



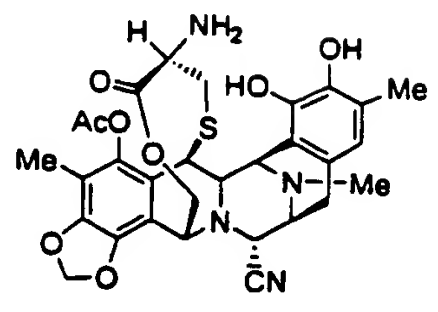
15 (10)



36 (5)



(23)



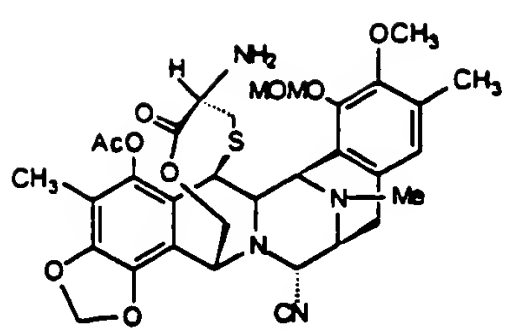
(24)

Compound (1) corresponds to the synthetic intermediate (47) described in the US patent No 5,721,362. Compounds 27 and 28 included in Table IV are described as 35 and 34 in WO 00/69862.

Some of the preferred methods of producing the compound of formula I are described below in the following reaction schemes with examples of typical substituent groups. These typical substituents are not limiting of the invention, and the process is to be understood in the more general sense, without special regard to the identities indicated by the code letters.

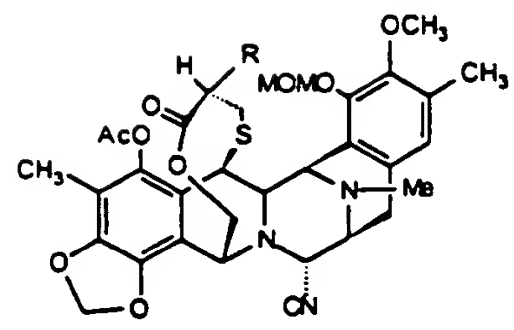
Numerous active antitumoral compounds have been prepared from this compounds and it is believed that many more compounds can be formed in accordance with the teachings of the present disclosure.

SCHEME I



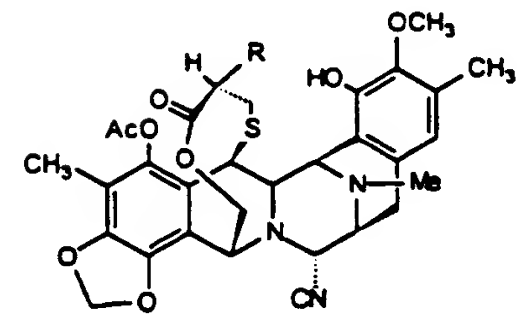
1

A or B or C
or D or E or F



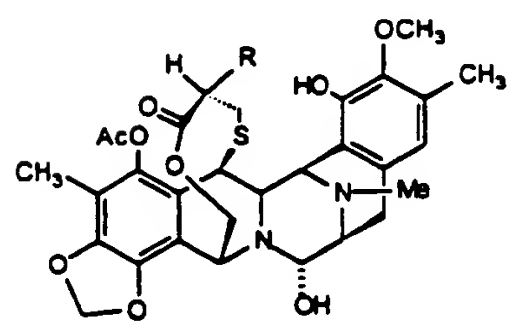
2a-n

G



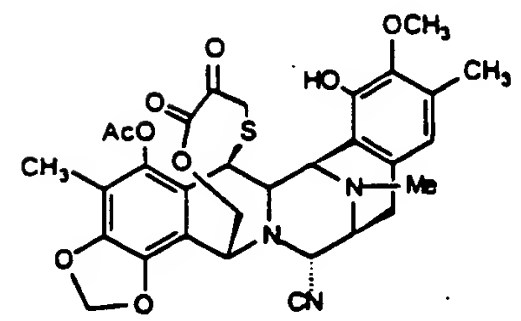
3a-n, 3o

I or J



4a-i, 4k-l, 4n, 4o

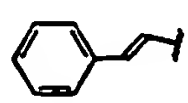
H



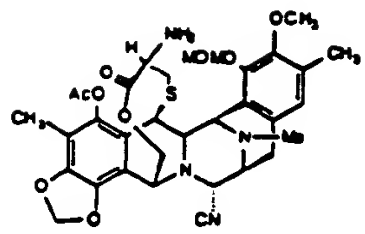
5

R:
- **a**: AcNH-
- **b**: F_3CCONH-
- **c**: $CH_3(CH_2)_2CONH$-
- **d**: $(CH_3)_2CHCH_2CONH$-
- **e**: $CH_3(CH_2)_6CONH$-
- **f**: $CH_3(CH_2)_{14}CONH$-
- **g**: BzNH-
- **h**: CinnCONH-
- **i**: p-F_3C-CinnCONH-
- **j**: PhtN-
- **k**: BiotinCONH-
- **l**: $HO_2CCH_2CH_2CONH$-
- **m**: $(CH_3)_2N$-
- **n**: BnNH-
- **o**: PrNH-

Cinn:

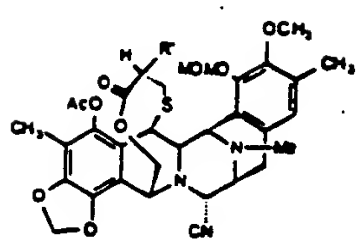


SCHEME II



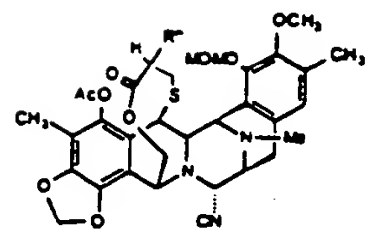
1

B



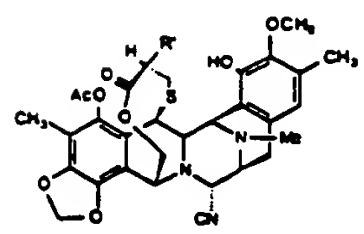
7, 8, 2w, 2y

K and B



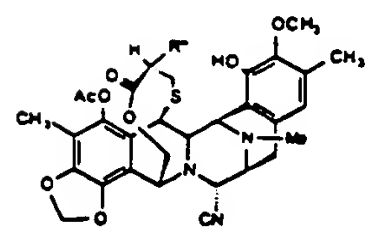
2t, 9

G



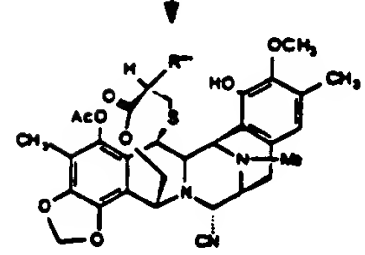
3p, 3v-w, 3y-z

G



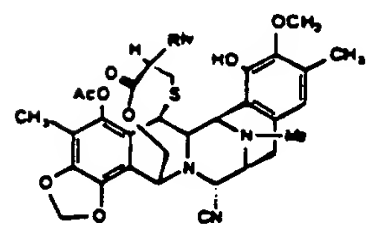
3s-t

E

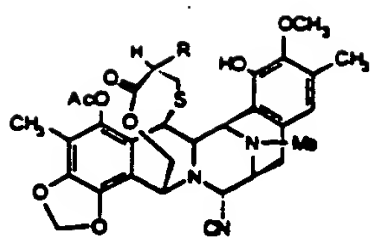


3q-r, 3x

E



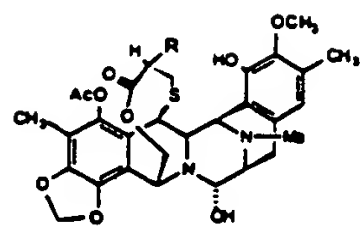
3u



3p-v, 3x-y

R= R', R", R"', R^{iv}

I or J

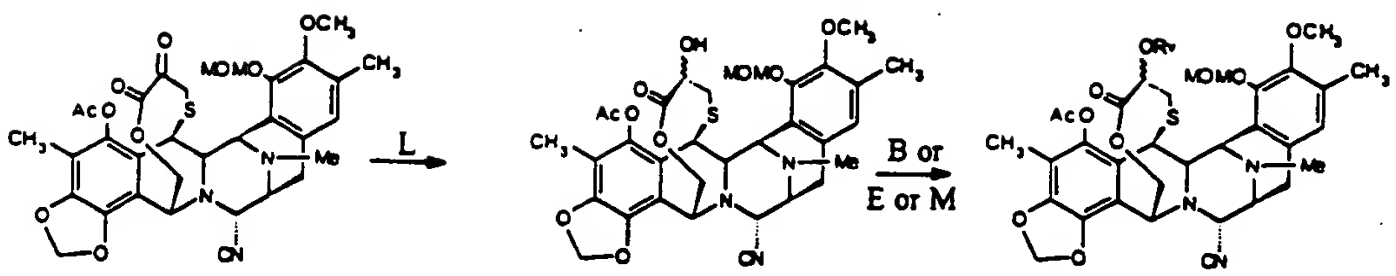


4p-v, 4x-y

R:

p: NH_2-ValCONH-
q: Ac-*N*-ValCONH-
r: CinnCO-*N*-ValCONH-
s: NH_2-Ala-ValCONH-
t: Ac-*N*-Ala-ValCONH-
u: CinnCO-*N*-Ala-ValCONH-
v: NH_2-AlaCONH-
w: Ac-*N*-AlaCONH-
x: CinnCO-*N*-AlaCONH-
y: $FmSCH_2CH(NHAlloc)CONH$-
z: $FmSCH_2CH(NH_2)CONH$-
7: Boc-*N*-ValCONH-
8: Boc-*N*-AlaCONH-
9: Boc-*N*-Ala-ValCONH

SCHEME III

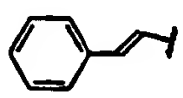


10 | 11, 12* | 13a-c, 13e-f, 13h, 13il, 14a*

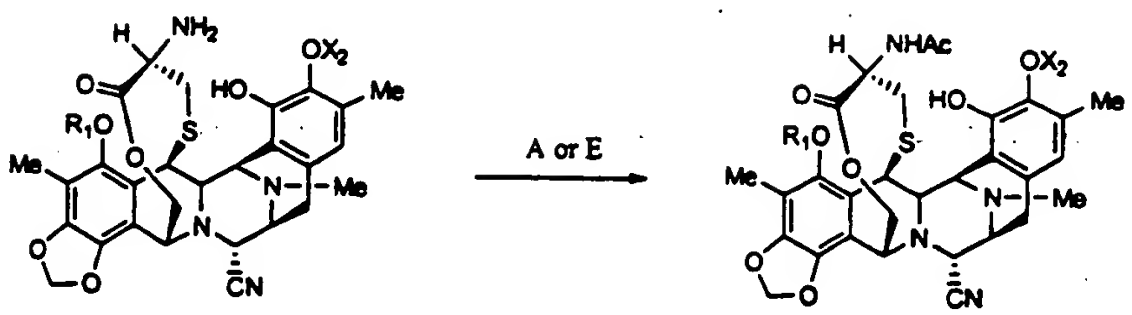
19, 21a, 21c, 21e-f, 21h, 21il, 22a* | 15, 16*, 17a-c, 17e-f, 17h, 17il, 18a*

R^v:
- a: Ac-
- b: F_3CCO-
- c: $CH_3(CH_2)_2CO$-
- e: $CH_3(CH_2)_6CO$-
- f: $CH_3(CH_2)_{14}CO$-
- h: CinnCO-
- il: $MeSO_2$-
- 15: H-
- 16: H-
- 19: H-

Cinn:



SCHEME IV



	R_1	X_2
23	H	Me
24	Ac	H

	R_1	X_2
25	H	Me
26	Ac	H

The type of reactions are the following:

Methods A, B, C, E and M include different acylation methods with acid chlorides, anhydrides, acids or sulfonyl chlorides, to obtain amide or ester bonds.

Methods D and H involve reductive alkylation reactions between an aldehyde and 1 or an amine and 5 to give 2m or 3o.

Method F transforms compound 1 to 2n by reaction with BnBr and Cs_2CO_3.

Method G involves the deprotection of methoxymethyl group (MOM) or MOM/tert-butyloxy carbonyl groups or MOM/allyloxy carbonyl groups using trimethylchlorosilane (TMSCl) and sodium iodide.

Methods I ($AgNO_3$) and J (CuBr) convert CN into OH in position C-21.

Method K involves the hydrolysis of a carbamate bond using aqueous trifluoroacetic acid.

Method L converts a carbonyl group to an alcohol by reduction with $NaCNBH_3$ in the presence of acetic acid. With this reaction a new chiral center is generated. Taking into account steric effects and spectroscopic data, it seem that the main compound (11) has R configuration at this center and the secondary product (12*) has S configuration. On this basis 13, 15, 17, 19, 21 will have R configuration and 14*, 18* and 22* will have S configuration. These assignments have been made based on the available spectral data and as such, in the absence of specific studies to confirm the assignments, should be considered as only tentative.

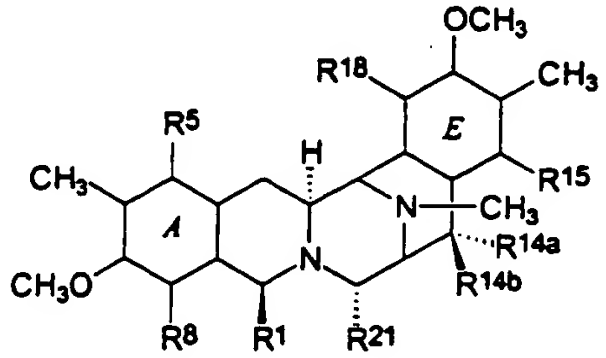
Modified processes can be used to prepare other compounds of this invention. In particular the starting material and/or reagents and reactions can be varied to suit other combinations of the substituent groups.

In another aspect, the present invention is directed at the use of a known compound, safracin B, also referred to as quinonamine, in hemisynthetic synthesis.

More generally, the invention relates to a hemisynthetic process for the formation of intermediates, derivatives and related structures of ecteinascidin or other tetrahydroisoquinolinephenol compounds starting from natural bis(tetrahydroisoquinoline) alkaloids.

Suitable preferred starting materials for the hemi-synthetic process include the classes of saframycin and safracin antibiotics available from different culture broths, and also the classes of reineramicin and xestomycin compounds available from marine sponges.

A general formula (XV) for the starting compounds is as follows:



where:

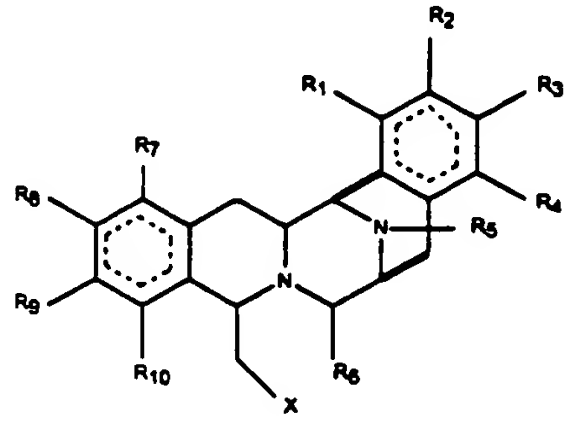
R^1 is an amidomethylene group such as $-CH_2-NH-CO-CR^{25a}R^{25b}R^{25c}$ where R^{25a} and R^{25b} form a keto group or one is -OH, $-NH_2$ or $-OCOCH_3$ and the other is $-CH_2COCH_3$, -H, -OH or $-OCOCH_3$, provided that when R^{25a} is -OH or $-NH_2$ then R^{25b} is not -OH, and R^{25c} is -H, $-CH_3$ or $-CH_2CH_3$, or R^1 is an acyloxymethylene group such as $-CH_2-O-CO-R$, where R is $-C(CH_3)=CH-CH_3$ or $-CH_3$;

R^5 and R^8 are independently chosen from -H, -OH or $-OCOCH_2OH$, or R^5 and R^8 are both keto and the ring *A* is a p-benzoquinone ring;

R^{14a} and R^{14b} are both -H or one is -H and the other is -OH, $-OCH_3$ or $-OCH_2CH_3$, or R^{14a} and R^{14b} together form a keto group;

R^{15} and R^{18} are independently chosen from -H or -OH, or R^5 and R^8 are both keto and the ring *A* is a p-benzoquinone ring; and
R^{21} is -OH or -CN.

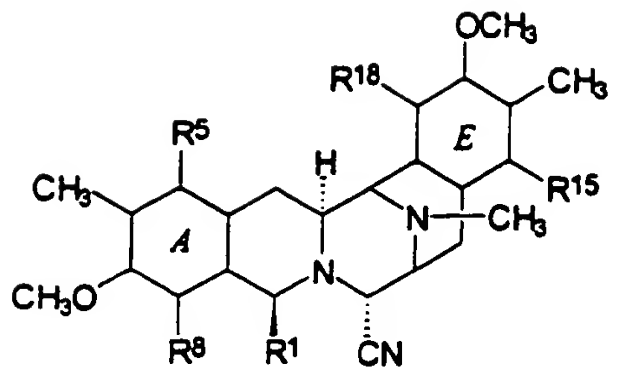
A more general formula for these class of compounds is provided below:



wherein the substituent groups defined by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} are each independently selected from the group consisting of H, OH, OCH_3, CN, =O, CH_3; wherein X are the different amide or ester functionalities contained in the mentioned natural products; wherein each dotted circle represents one, two or three optional double bonds.

Thus, according to the present invention, we now provide hemisynthetic routes for the production of new and known compounds. The hemisynthetic routes of the invention each comprise a number of transformation steps to arrive at the desired product. Each step in itself is a process in accordance with this invention. The invention is not limited to the routes that are exemplified, and alternative routes may be provided by, for example, changing the order of the transformation steps, as appropriate.

In particular, this invention involves the provision of a 21-cyano starting material of general formula (XVI):



where R^1, R^5, R^8, R^{14a}, R^{14b}, R^{15} and R^{18} are as defined.

Other compounds of formula (XVI) with different substituents at the 21-position may also represent possible starting materials. In general, any derivative capable of production by nucleophilic displacement of the 21-hydroxy group of compounds of formula (XV) wherein R^{21} is a hydroxy group is a candidate. Examples of suitable 21-substituents include but are not limited to:

a mercapto group;

an alkylthio group (the alkyl group having from 1 to 6 carbon atoms);

an arylthio group (the aryl group having from 6 to 10 carbon atoms and being unsubstituted or substituted by from 1 to 5 substituents selected from, for example, alkyl group having from 1 to 6 carbon atoms, alkoxy groups having from 1 to 6 carbon atoms, halogen atoms, mercapto groups and nitro groups);

an amino group;

a mono-or dialkylamino (the or each alkyl group having from 1 to 6 carbon atoms);

a mono-or diarylamino group (the or each aryl group being as defined above in relation to arylthio groups);

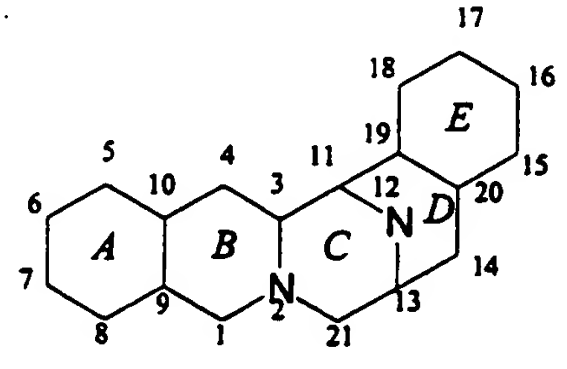
an α-carbonylalkyl group of formula $-C(R^a)(R^b)-C(=O)R^c$, where

R^a and R^b are selected from hydrogen atoms, alkyl groups having from 1 to 20 carbon atoms, aryl groups (as defined above in relation to arylthio groups) and aralkyl groups (in which an alkyl group having from 1 to 4 carbon atoms is substituted by an aryl group a defined above in relation to arylthio groups), with the proviso that one of R^a and R^b is a hydrogen atom;

R^c is selected from a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, aryl groups (as defined above in relation to arylthio groups), an aralkyl group (in

which an alkyl group having from 1 to 4 carbon atoms is substituted by an aryl group a defined above in relation to arylthio groups), an alkoxy group having from 1 to 6 carbon atoms, an amino group or a mono- or dialkylamino group as defined above.

Thus, in a more general aspect, the present invention relates to processes where the first step is to form a 21-deriviative using a nucleophilic reagent. We refer to such compounds as 21-Nuc compounds. Preferred starting material 21-Nuc compounds have the structure of formula (XIV):



where at least one ring *A* or *E* is quinolic.

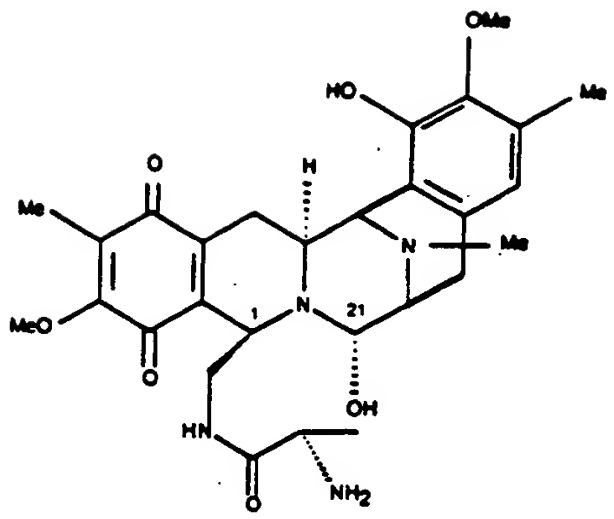
Thus, in addition to the use of 21-cyano compounds, processes using other nucleophile-containing compounds, to produce similar compounds of formula (XVI) wherein the 21-position is protected by another nuclephilic group, a 21-Nuc group, are also envisaged. For example, a 21-Nuc compound of formula (XVI) with an alkylamino substituent at the 21-position can be produced by reacting the compound of formula (XV) wherein R^{21} is a hydroxy group with a suitable alkylamine. A 21-Nuc compound of formula (XVI) with an alkylthio substituent at the 21-position can also be produced by reacting the compound of formula (XV) wherein R^{21} is a hydroxy group with a suitable alkanethiol. Alternatively, a 21-Nuc compound of formula (XVI) with an α-carbonylalkyl substituent at the 21-position can be produced by reacting the compound of formula (XV) wherein R21 is a hydroxy group with a suitable carbonyl compound, typically in the presence of a base. Other routes are available for other 21-Nuc compounds.

The presence of the 21-cyano group is required for some of the end-products, notably ecteinascidin 770 and phthalascidin, while for other end-products it acts as a protecting group which can readily be converted to another substituent, such as the 21-hydroxy group. The adoption of the 21-cyano compound as the starting material effectively stabilises the molecule during the ensuing synthetic steps, until it is optionally removed. Other 21-Nuc compounds can offer this and other advantages.

Preferred starting materials include those compounds of formula (XV) or (XVI) where R^{14a} and R^{14b} are both hydrogen. Preferred starting materials also include compounds of formula (XV) or (XVI) where R^{15} is hydrogen. Furthermore, the preferred starting materials include compounds of formula (XV) or (XVI) where ring *E* is a phenolic ring. Preferred starting materials further include compounds of formula (XV) or (XVI) where at least one, better at least two or three of R^5, R^8, R^{15} and R^{18} is not hydrogen.

Examples of suitable starting materials for this invention include saframycin A, saframycin B, saframycin C, saframycin G, saframycin H, saframycin S, saframycin Y_3, saframycin Yd_1, saframycin Ad_1, saframycin Yd_2, saframycin AH_2, saframycin AH_2Ac, saframycin AH_1, saframycin AH_1Ac, saframycin AR_3, renieramycin A, renieramycin B, renieramycin C, renieramycin D, renieramycin E, renieramycin F, xestomycin, saframycin D, saframycin F, saframycin Mx-1, saframycin Mx-2, safracin A, safracin B and saframycin R. Preferred starting materials have a cyano group in position 21, for the group R^{21}.

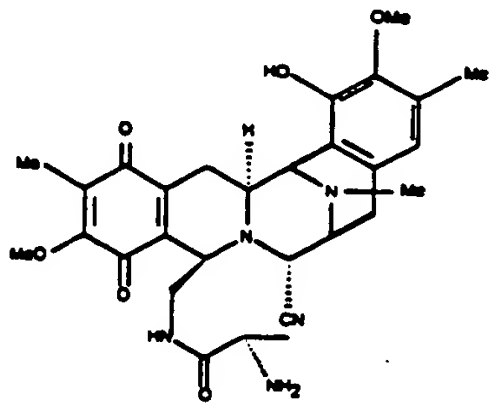
In a particularly preferred aspect, the invention involves a hemisynthetic process wherein the transformation steps are applied to safracin B:



SAFRACIN B

Safracin B presents a ring system closely related to the ecteinascidins. This compound has the same pentacycle structure and the same substitution pattern in the right-hand aromatic ring, ring *E*.

The more preferred starting materials of this invention have a 21-cyano group. The currently most preferred compound of the present invention is the compound of Formula **2**. This compound is obtained directly from safracin B and is considered a key intermediate in the hemisynthetic process.



compound 2

Cyanosafracin B by fermentation of a safracin B-producing strain of *Pseudomonas fluorescens*, and working up the cultured broth using cyanide ion. The preferred strain of *Pseudomonas fluorescens* is strain A2-2, FERM BP-14, which is employed in the procedure of EP-A-055 299. A suitable source of cyanide ion is potassium cyanide. In a typical work-up, the broth is filtered and excess cyanide ion is

added. After an appropriate interval of agitation, such as 1 hour, the pH is rendered alkaline, say pH 9.5, and an organic extraction gives a crude extract which can be further purified to give the cyanosafracin B.

In general, the conversion of the 21-cyano starting compound to an product of this invention involves:

a) conversion if necessary of a quinone system for the ring *E* into the phenol system

b) conversion if necessary of a quinone system for the ring *A* into the phenol system;

c) conversion of the phenol system for the ring *A* into the methylenedioxyphenol ring;

d) formation of the bridged spiro ring system of formula (IV), (VI) or (VII) across the 1-position and 4-position in ring *B*; and

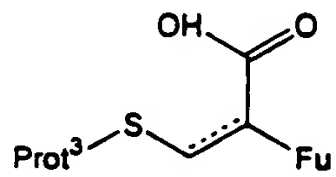
e) derivatisation as appropriate, such as acylation.

Step (a), conversion if necessary of a quinone system for the ring *E* into the phenol system, can be effected by conventional reduction procedures. A suitable reagent system is hydrogen with a palladium-carbon catalyst, though other reducing systems can be employed.

Step (b), conversion if necessary of a quinone system for the ring *A* into the phenol system is analogous to step (a), and more detail is not needed.

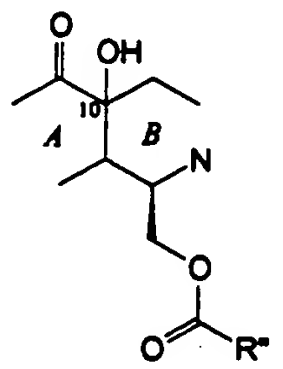
Step (c), conversion of the phenol system for the ring *A* into the methylenedioxyphenol ring, can be effected in several ways, possibly along with step (b). For example, a quinone ring A can be demethylated in the methoxy substituent at the 7-position and reduced to a dihydroquinone and trapped with a suitable electrophilic reagent such as CH_2Br_2, $BrCH_2Cl$, or a similar divalent reagent directly yielding the methylenedioxy ring system, or with a divalent reagent such as thiocarbonyldiimidazol which yields a substituted methylenedioxy ring system which can be converted to the desired ring.

Step (d) is typically effected by appropriate substitution at the 1-position with a bridging reagent that can assist formation of the desired bridge, forming an exendo quinone methide at the 4-position and allowing the methide to react with the 1-substituent to bring about the bridged structure. Preferred bridging reagents are of formula (XIX)

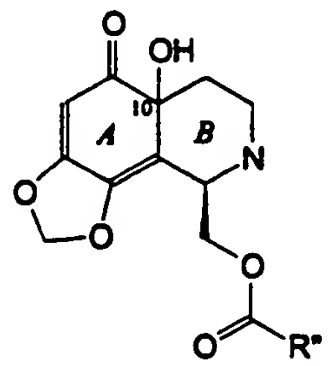


where Fu indicates a protected functional group, such as a group -NHProt^{4a} or OProt^{4b}, Prot^3 is a protecting group, and the dotted line shows an optional double bond.

Suitably the methide is formed by first introducing a hydroxy group at the 10-position at the junction of rings *A* and *B* to give a partial structure of formula (XX):



or more preferably a partial structure of formula (XXI):

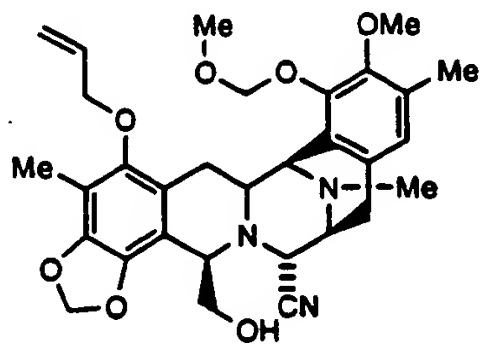


where the group R" is chosen for the desired group of formula (IV), (V), (VI) or (VII). For the first two such groups, the group R" typically takes the form -CHFu-CH_2-SProt^3. The protecting groups can then be removed and modified as appropriate to give the desired compound.

A typical procedure for step (d) is provided in US Patent 5,721,362 incorporated by reference. Particular reference is made to the passage at column 8, step (l) and Example 33 of the US Patent, and related passages.

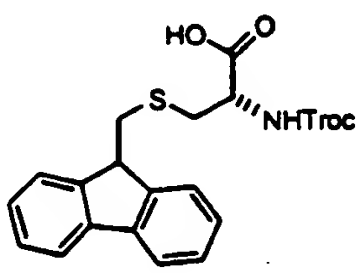
Derivatisation in step (e) can include acylation, for instance with a group R^a-CO- as well as conversion of the 12-NCH_3 group to 12-NH or 12-NCH_2CH_3. Such conversion can be effected before or after the other steps, using available methods.

By way of illustration, can be transformed into Intermediate **25**;

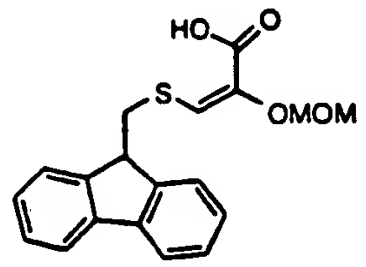


INT-25

and from this derivative it is possible to introduce a number of cysteine derivatives that can be transformed into compounds of this invention. Preferred cysteine derivatives are exemplified by the following two compounds:



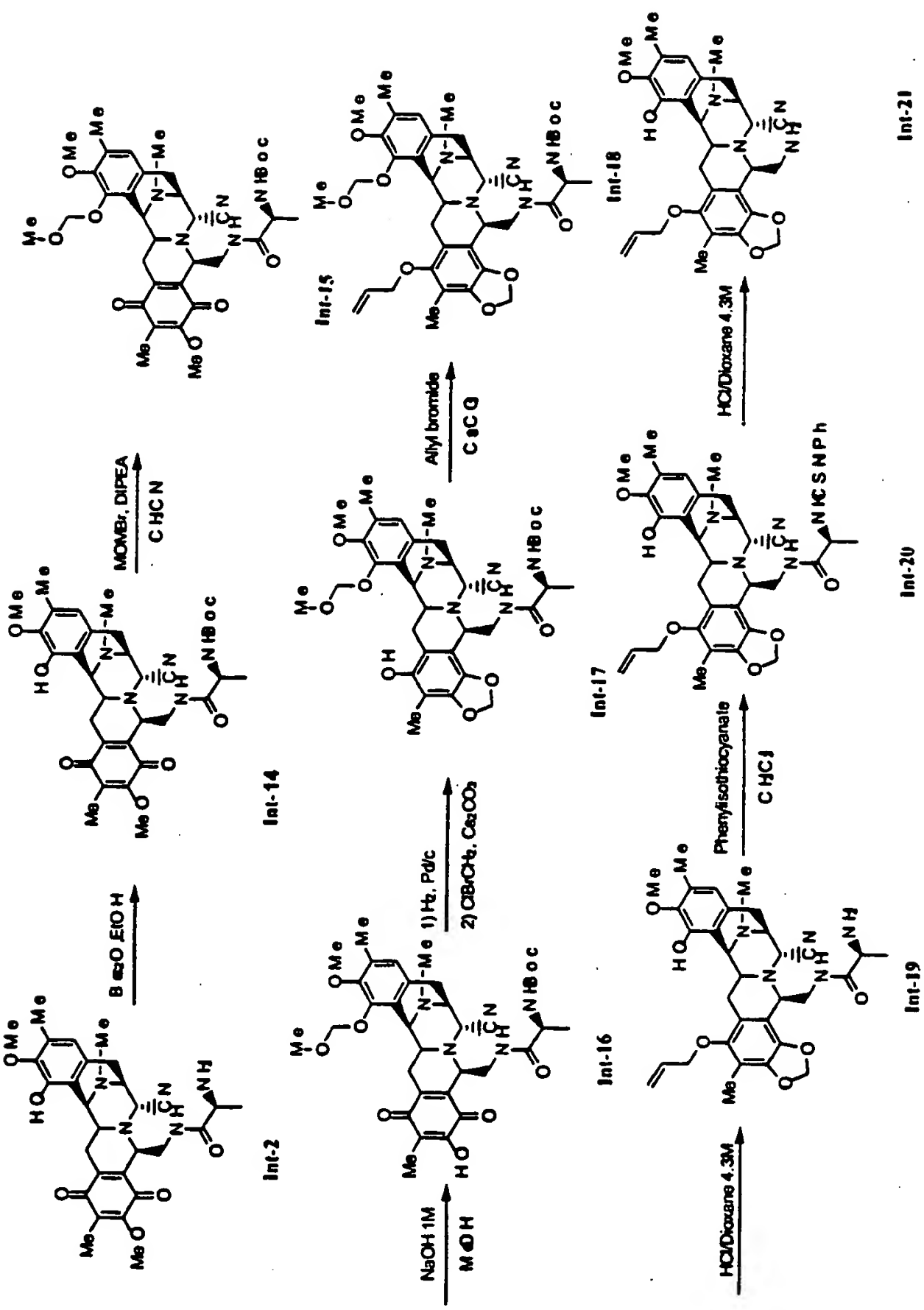
Int-29

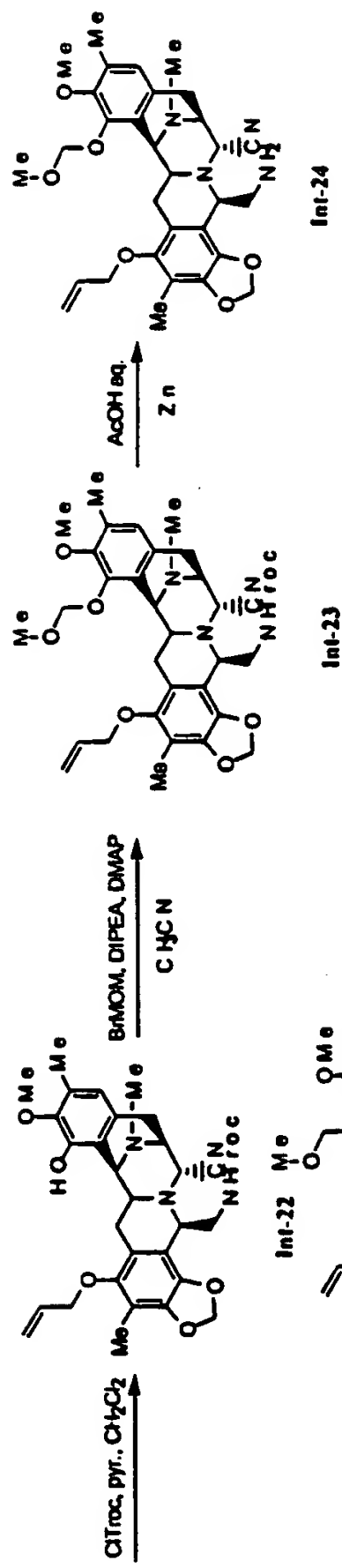


Int-37

One method of this invention transforms cyanosafracin B into intermediate **Int-25** through a sequence of reactions that involves essentially (1) removal of methoxy group placed in ring A, (2) reduction of ring A and formation of methylene-dioxy group in one pot, (3) hydrolysis of amide function placed over carbon 1, (4) transformation of the resulting amine group into hydroxyl group, see scheme V.

Scheme V


Int-2
Int-14
Int-15
Int-18
Int-21
Int-16
Int-17
Int-19
Int-20
Ac2O EtOH
MOMBr, DIPEA
CH3CN
Allyl bromide
CsCO
HCl/Dioxane 4.3M
NaOH 1M
MeOH
1) H2, Pd/c
2) OBzCH2, Cs2CO3
Phenylisothiocyanate
CHCl


Int-24
AcOH aq.
Zn
Int-23
BrMOM, DIPEA, DMAP
CH3CN
Int-22
ClTroc, pyr., CH2Cl2
Int-25
H2O, THF:cOH
NMO

The method avoids protection and de-protection of the primary alcohol function at the position 1 in ring B of compound **Int-25** using directly a cysteine residue **Int-29** to form intermediate **Int-27**. Cysteine derivative **Int-29** is protected in the amino group with β-β-β-trichloroethoxycarbonyl protecting group in order to have compatibility with the existing allyl and MOM groups. Intermediate **Int-27** is directly oxidized and cycled. These circumstances, together with a different de-protecting strategy in the later stages of the synthesis makes the route novel and more amenable to industrial development than the process of US 5,721,362.

The conversion of the 2-cyano compound into Intermediate **Int-25** usually involves the following steps (see scheme V):

formation of the protected compound of Formula **Int-14** by reacting **Int-2** with *tert*-butoxycarbonyl anhydride;

converting of **Int-14** into the di-protected compound of Formula **Int-15** by reacting with bromomethylmethyl ether and diisopropylethylamine in acetonitrile;

selective elimination of the methoxy group of the quinone system in **Int-15** to obtain the compound of Formula **Int-16** by reacting with a methanolic solution of sodium hydroxide;

transforming of Int-16 into the methylene-dioxy compound of Formula **Int-18** by employing the next preferred sequence: (1) quinone group of compound **Int-16** is reduced with 10% Pd/C under hydrogen atmosphere; (2) the hydroquinone intermediate is converted into the methylenedioxy compound of Formula **Int-17** by reacting with bromochloromethane and caesium carbonate under hydrogen atmosphere; (3) **Int-17** is transformed into the compound of Formula **Int-18** by protecting the free hydroxyl group as a OCH_2R group. This reaction is carried out with $BrCH_2R$ and caesium carbonate, where R can be aryl, $CH=CH_2$, OR′ etc.

elimination of the *tert*-butoxycarbonyl and the methyloxymethyl protecting groups of **Int-18** to afford the compound of Formula **Int-19** by reacting with a solution of HCl in dioxane. Also this reaction is achieved by mixing **Int-18** with a solution of trifluoroacetic acid in dichloromethane;

formation of the thiourea compound of Formula **Int-20** by reacting **Int-19** with phenylisothiocyanate;

converting compound of Formula **Int-20** into the amine compound of Formula **Int-21** by reacting with a solution of hydrogen chloride in dioxane;

transforming compound of Formula **Int-21** into the *N*-Troc derivative **Int-22** by reacting with trichloroethyl chloroformate and pyridine;

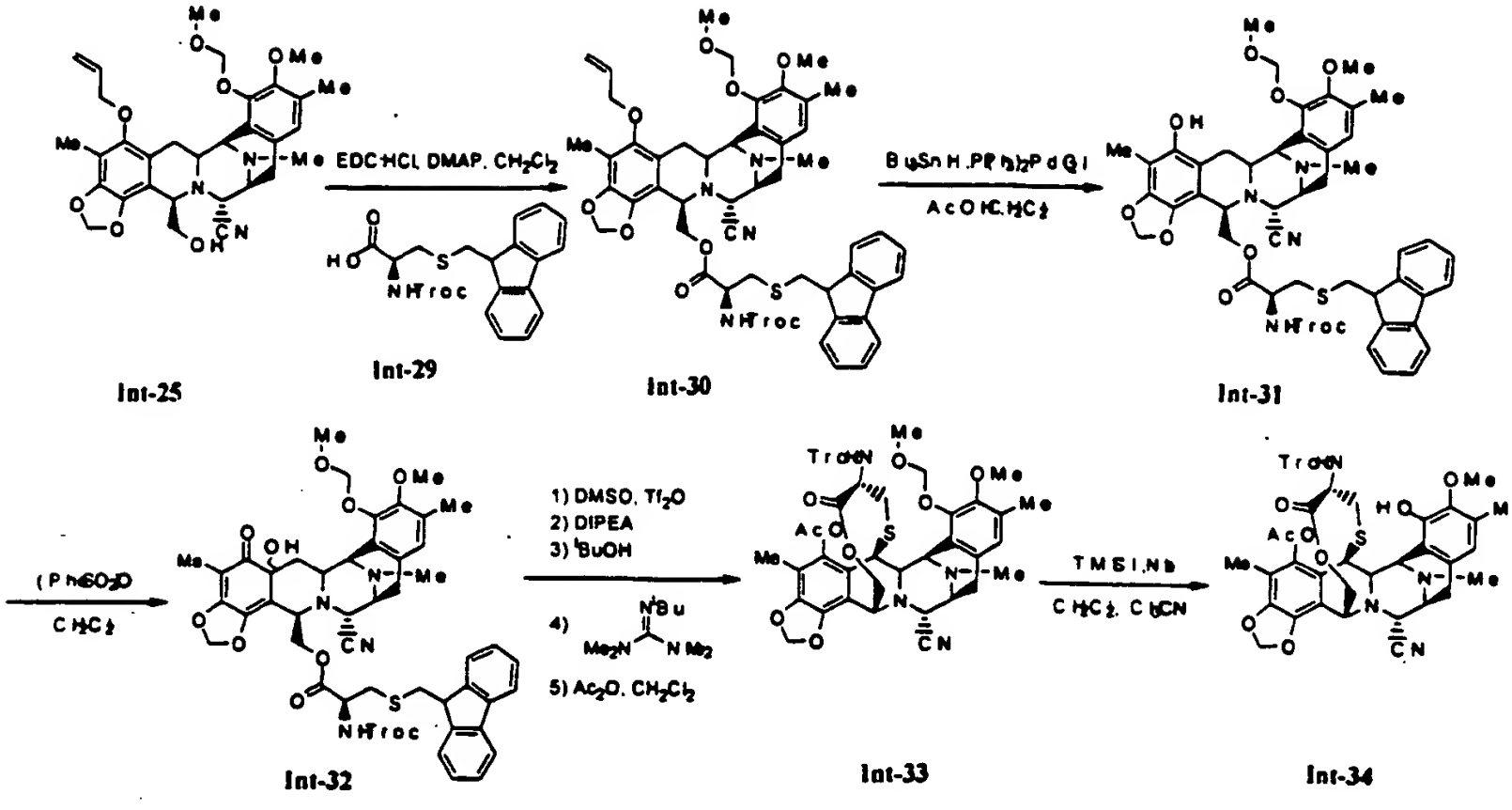
formation of the protected hydroxy compound of Formula **Int-23** by reacting **Int-22** with bromomethylmethyl ether and diisopropylethylamine;

transforming compound of Formula **Int-23** into the *N*-H derivative **Int-24** by reacting with acetic acid and zinc;

conversion of compound of Formula **Int-24** into the hydroxy compound of Formula **Int-25** by reaction with sodium nitrite in acetic acid. Alternatively, it can be used nitrogen tetroxide in a mixture of acetic acid and acetonitrile followed by treatment with sodium hydroxide. Also, it can be used sodium nitrite in a mixture of acetic anhydride-acetic acid, followed by treatment with sodium hydroxide.

From intermediate **Int-25** the conversion into final intermediate compounds **Int-35** or **Int-36** of this invention can then proceed as shown in Scheme VI:

Scheme VI



transforming compound of formula **Int-24** into the derivative **Int-30** by protecting the primary hydroxyl function with (S)-N-2,2,2-tricloroethoxycarbonyl-S-(9H-fluoren-9-ylmethyl)cysteine **Int-29**;

converting the protected compound of formula **Int-30** into the phenol derivative **Int-31** by cleavage of the allyl group with tributyltin hydride and dichloropalladium-bis (triphenylphosphine);

transforming the phenol compound of Formula **Int-31** into compound of formula **Int-32** by oxidation with benzeneseleninic anhydride at low temperature;

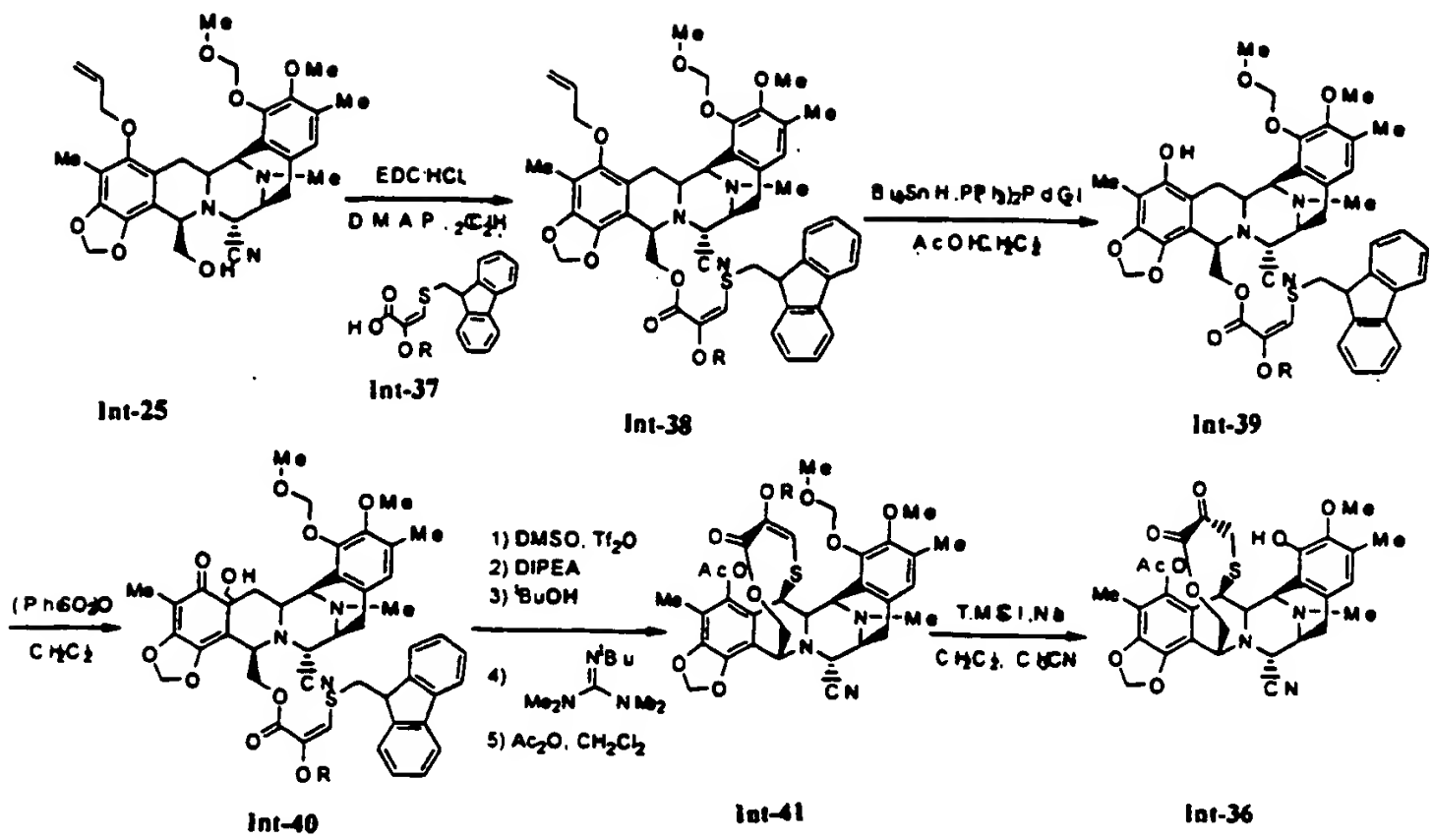
transforming the hydroxy compound of formula **Int-32** into the lactone **Int-33** by the following sequence: (1) Reacting compound of formula **Int-32** with 2 eq. of triflic anhydride and 5 eq. of DMSO. (2) followed by reaction with 8 eq. of diisopropylethylamine. (3) followed by reaction with 4 eq of t-butyl alcohol (4) followed by reaction with 7 eq of 2-*tert*-Butyl-1,1,3,3,tetramethylguanidine (5) followed by reaction with 10 eq of acetic anhydride;

transforming the lactone compound **Int-33** into hydroxyl compound **Int-34** by removal of MOM protecting group with TMSI;

cleaving the N-trichloroethoxycarbonyl group of the compound of formula **Int-34** into compound **Int-35** by reaction with Zn/AcOH;

transforming the amino compound **Int-35** into the corresponding α-keto lactone compound **Int-36** by reaction with N-methyl pyridinium carboxaldehyde chloride followed by DBU;

The conversion of the Intermediate compound **Int-25** into ET-743 using cysteine derivative **Int-37** can be made in a similar manner and with the same reagents than with cysteine derivative **Int-29** with the exception of transformations (f) and (g). The reaction sequence is exemplified in the following Scheme VII:



Scheme VII

It will readily be appreciated that these synthetic routes can readily be modified, particularly by appropriate change of the starting material and reagents, so as to provide compounds of this invention with different fused ring systems or different substituents.

NOVEL ACTIVE COMPOUNDS

We have found that compounds of the invention have activity in the treatment of cancers, such as leukaemias, lung cancer, colon cancer, kidney cancer and melanoma.

Thus, the present invention provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of a compound of the invention, or a pharmaceutical composition thereof.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient a compound or compounds of the invention, as well as the processes for their preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carbonplatin, oxaliplatin, paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics;

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine;

m) steroid analogues, in particular dexamethasone;

n) anti-inflammatory drugs, in particular dexamethasone; and

o) anti-emetic drugs, in particular dexamethasone.

The present invention also extends to the compounds of the invention for use in a method of treatment, and to the use of the compounds in the preparation of a composition for treatment of cancer.

CYTOTOXIC ACTIVITY

Cell Cultures. Cells were maintained in logarithmic phase of growth in Eagle's Minimum Essential Medium, with Earle's Balanced Salts, with 2.0 mM L-glutamine, with non-essential amino acids, without sodium bicarbonate (EMEM/neaa); supplemented with 10% Fetal Calf Serum (FCS), 10^{-2} M sodium bicarbonate and 0.1 g/l penicillin-G + streptomycin sulfate.

A simple screening procedure has been carried out to determine and compare the antitumour activity of these compounds, using an adapted form of the method described by Bergeron et al (1984). The tumour cell line employed have been P-388 (suspension culture of a lymphoid neoplasm from DBA/2 mouse), A-549 (monolayer culture of a human lung carcinoma), HT-29 (monolayer culture of a human colon carcinoma) and MEL-28 (monolayer culture of a human melanoma).

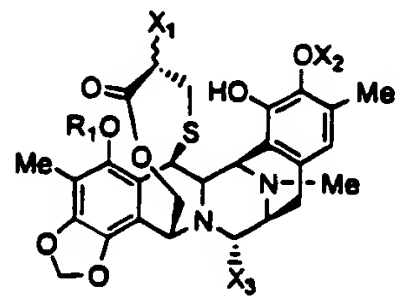
P-388 cell were seeded into 16 mm wells at $1x10^4$ cells per well in 1 ml aliquots of MEM 5FCS containing the indicated concentration of drug. A separate set of cultures without drug was seeded as control growth to ensure that cells remained in exponential phase of growth. All determinations were carried out in duplicate. After three days of incubation at 37°C, 10% CO_2 in a 98% humid atmosphere, an approximately IC_{50} was determined by comparing the growth in wells with drug to the growth in wells control.

A-549, HT-29 and MEL-28 were seeded into 16 mm wells at $2x10^4$ cells per well in 1 ml aliquots of MEM 10FCS containing the indicated concentration of drug. A separate set of cultures without drug was seeded as control growth to ensure that cells remained in exponential phase of growth. All determinations were carried out in duplicate. After three days of incubation at 37°C, 10% CO_2 in a 98% humid atmosphere, the wells were stained with 0.1% Crystal Violet. An approximately IC_{50} was determined by comparing the growth in wells with drug to the growth in wells control.

1. Raymond J. Bergeron, Paul F. Cavanaugh, Jr., Steven J. Kline. Robert G. Hughes, Jr., Gary T. Elliot and Carl W. Porter. Antineoplastic and antiherpetic activity of spermidine catecholamide iron chelators. *Biochem. Bioph. Res. Comm. 1984, 121*(3), 848-854.

2. Alan C. Schroeder, Robert G. Hughes, Jr. and Alexander Bloch. Effects of Acyclic Pyrimidine Nucleoside Analoges. *J. Med. Chem.* 1981, 24 1078-1083.

Examples of biological activities of the compounds described in the present application are in Table IV (IC_{50} (ng/mL)) on the following pages.



Compound	X_1	X_2	X_3	R_1	P-388	A-549	HT-29	MEL-28	DU-145
4a	AcNH-	Me	OH	Ac	0.1	0.5	0.1	0.5	0.1
4b	F_3CCONH-	Me	OH	Ac	0.5	0.5	0.5	0.5	0.5
4c	$CH_3(CH_2)_2CONH$-	Me	OH	Ac	0.1	0.1	0.1	0.1	0.1
4d	$(CH_3)_2CHCH_2CONH$-	Me	OH	Ac	0.5	0.5	0.5	0.5	0.5
4e	$CH_3(CH_2)_6CONH$-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
4f	$CH_3(CH_2)_{14}CONH$-	Me	OH	Ac	100	100	100	100	100
4g	PhCONH-	Me	OH	Ac	0.1	0.5	0.5	0.5	0.5
4h	CinnCONH-	Me	OH	Ac	0.5	0.5	0.5	0.5	0.5
4i	p-F_3C-CinnCONH-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
4k	BiotinCONH-	Me	OH	Ac	10	10	10	10	10
4l	$HO_2CCH_2CH_2CONH$-	Me	OH	Ac	100	100	100	100	100
4n	BnNH-	Me	OH	Ac	0.5	0.5	0.5	0.5	0.5
4o	PrNH-	Me	OH	Ac		1.0	1.0		
4p	NH_2-ValCONH-	Me	OH	Ac	0.5	0.5	0.5	0.5	0.5
4q	Ac-N-ValCONH-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
4r	CinnCO-N-ValCONH-	Me	OH	Ac	0.5	0.5	0.5	0.5	0.5
4s	NH_2-Ala-ValCONH-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
4t	Ac-N-Ala-ValCONH-	Me	OH	Ac	100	100	10	10	10
4u	CinnCO-N-Ala-ValCONH-	Me	OH	Ac	5.0	5.0	5.0	5.0	5.0
4v	NH_2-AlaCONH-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
4x	CinnCO-N-AlaCONH-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
4y	$FmSCH_2CH(NHAlloc)CONH$-	Me	OH	Ac	50	50	50	50	50
19	HO-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0

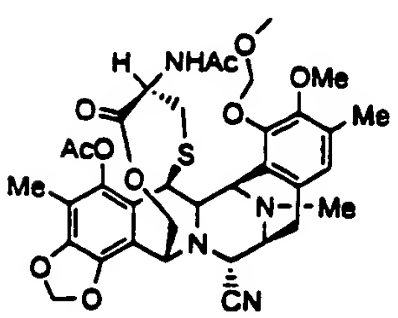
21a	AcO-	Me	OH	Ac	0.5	1.0	1.0	1.0	1.0
21c	$CH_3(CH_2)_2COO$-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
21e	$CH_3(CH_2)_6COO$-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
21f	$CH_3(CH_2)_{14}COO$-	Me	OH	Ac		>1000	>1000		
21h	CinnCOO-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
21l	$MeSO_3$-	Me	OH	Ac	1.0	1.0	1.0	1.0	1.0
22a*	*AcO-	Me	OH	Ac		1.0	1.0		
27	NH_2	Me	CN	Ac	5.0	5.0	5.0	5.0	--
23	NH_2	Me	CN	H		10	10		
24	NH_2	H	CN	Ac		100	100		
3a	AcNH-	Me	CN	Ac	0.5	0.5	0.5	0.5	0.5
25	AcNH-	Me	CN	H		10	10		
26	AcNH-	H	CN	Ac		100	100		
3b	F_3CCONH-	Me	CN	Ac	1.0	1.0	1.0	1.0	1.0
3c	$CH_3(CH_2)_2CONH$-	Me	CN	Ac	0.1	0.1	0.1	0.1	0.1
3d	$(CH_3)_2CHCH_2CONH$-	Me	CN	Ac	0.1	0.1	0.1	0.1	0.1
3e	$CH_3(CH_2)_6CONH$-	Me	CN	Ac	1.0	1.0	1.0	1.0	1.0
3f	$CH_3(CH_2)_{14}CONH$-	Me	CN	Ac	$>1\cdot10^3$	$>1\cdot10^3$	$>1\cdot10^3$	$>1\cdot10^3$	$>1\cdot10^3$
3g	PhCONH-	Me	CN	Ac	0.1	0.1	0.1	0.1	0.1
3h	CinnCONH-	Me	CN	Ac	0.5	0.5	0.5	0.5	0.5
3i	p-F_3C-CinnCONH-	Me	CN	Ac	5.0	5.0	5.0	5.0	5.0
3j	PhtN-	Me	CN	Ac	5	5	5	5	5
6	2-MeO_2C-C_6H_4-CONH-	Me	CN	Ac	1	1	1	1	1
3k	BiotinNH-	Me	CN	Ac	10	10	5	5	5
3l	$HO_2C(CH_2)_2CONH$-	Me	CN	Ac	100	100	100	100	100

3m	$(CH_3)_2N$-	Me	CN	Ac	10	10	10	10	10
3n	BnNH-	Me	CN	Ac	0.5	0.5	0.5	0.5	0.5
3o	PrNH-	Me	CN	Ac		5	5		
3p	NH_2-ValCONH-	Me	CN	Ac	1	1	1	1	1
3q	Ac-N-ValCONH-	Me	CN	Ac	1	1	1	1	1
3r	CinnCO-N-ValCONH-	Me	CN	Ac	1	1	1	1	1
3s	NH_2-Ala-ValCONH-	Me	CN	Ac	1	1	1	1	1
3t	Ac-N-Ala-ValCONH-	Me	CN	Ac	10	10	10	10	10
3u	CinnCO-N-Ala-ValCONH-	Me	CN	Ac	5	5	1	1	1
3v	NH_2-AlaCONH-	Me	CN	Ac	1	1	1	1	1
3w	Ac-N-AlaCONH-	Me	CN	Ac	1	1	1	1	1
3x	CinnCO-N-AlaCONH-	Me	CN	Ac	0.1	0.1	0.1	0.1	0.1
3y	$FmSCH_2CH(NHAlloc)CONH$-	Me	CN	Ac	10	10	10	50	50
3z	$FmSCH_2CH(NH_2)CONH$-	Me	CN	Ac	50	50	50	50	50
28	Cl_3CCH_2OCONH-	Me	CN	Ac	1.0	1.0	1.0	1.0	1.0
15	HO-	Me	CN	Ac	5	5	5	5	5
16*	*HO-	Me	CN	Ac		10	10		
17a	AcO-	Me	CN	Ac	0.1	0.1	0.1	0.1	0.1
17b	F_3CCOO-	Me	CN	Ac	5.0	5.0	5.0	5.0	5.0
17c	$CH_3(CH_2)_2COO$-	Me	CN	Ac	1.0	1.0	1.0	1.0	1.0
17e	$CH_3(CH_2)_6COO$-	Me	CN	Ac	1.0	1.0	1.0	1.0	1.0
17f	$CH_3(CH_2)_{14}COO$-	Me	CN	Ac	>1000	>1000	>1000	>1000	>1000
17h	CinnCOO-	Me	CN	Ac	0.1	0.1	0.1	0.1	0.1
17ll	$MeSO_3$-	Me	CN	Ac	1	1	1	1	--
18a*	*AcO-	Me	CN	Ac	1.0	1.0	1.0	1.0	1.0

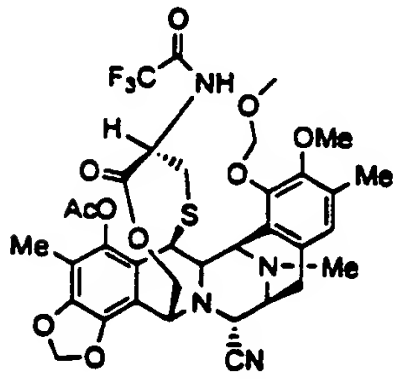
EXAMPLES

Example 1

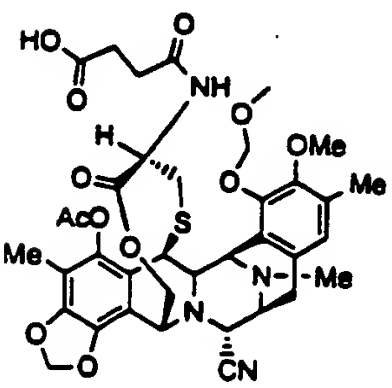
Method A: To a solution of 1 equiv. of **1** (**23** for **25**) coevaporated with anhydrous toluene in CH_2Cl_2 (0.08M) under Argon were added 1.2 equiv. of the anhydride. The reaction was followed by TLC and quenched with acid or base, extracted with CH_2Cl_2 and the organic layers dried with Na_2SO_4. Flash chromatography gives pure compounds.



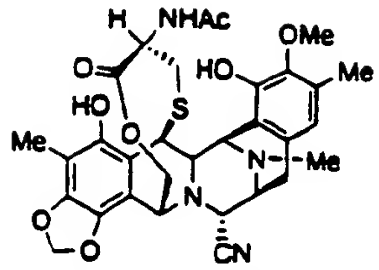
Compound **2a** (using Ac_2O as the anhydride): ^1H NMR (300 MHz, $CDCl_3$): δ 6.77 (s, 1H), 6.04 (dd, 2H), 5.53 (bd, 1H), 5.18 (dd, 2H), 5.02 (d, 1H), 4.58 (ddd, 1H), 4.52 (bs, 1H), 4.35 (d, 1H), 4.27 (s, 1H), 4.19-4.15 (m, 2H), 3.75 (s, 3H), 3.55 (s, 3H), 3.54-3.43 (m, 2H), 2.93 (bd, 2H), 2.35-2.02 (m, 2H), 2.28 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H), 2.02 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 168.7, 168.4, 149.7, 148.5, 145.8, 141.0, 140.4, 131.0, 130.5, 125.7, 124.5, 120.3, 117.9, 113.5, 113.4, 102.0, 99.1, 61.4, 60.3, 59.6, 58.8, 55.0, 54.5, 52.1, 41.8, 41.3, 32.6, 23.7, 20.9, 20.2, 16.1, 9.5; ESI-MS m/z: Calcd. for $C_{35}H_{40}N_4O_{10}S$: 708.2. Found ($M+H^+$): 709.2.



Compound **2b** (using $(F_3CCO)_2O$ as the anhydride): ^1H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.41 (bd, 1H), 6.05 (dd, 2H), 5.17 (dd, 2H), 5.05 (d, 1H), 4.60 (bp, 1H), 4.54-4.51 (m, 1H), 4.36-4.32 (m, 2H), 4.25-4.19 (m, 2H), 3.72 (s, 3H), 3.56 (s, 3H), 3.48-3.43 (m, 2H), 2.99-2.82 (m, 2H), 2.46-2.41 (m, 1H), 2.30-2.03 (m, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 168.5, 156.3, 155.8, 155.3, 149.3, 148.5, 146.0, 141.2, 140.6, 132.0, 130.2, 124.8, 120.2, 117.9, 113.2, 102.1, 99.2, 61.5, 60.6, 59.7, 59.1, 58.7, 57.5, 54.9, 54.6, 52.9, 42.0, 41.4, 31.6, 23.8, 20.2, 14.1, 9.6; ESI-MS m/z: Calcd. for $C_{35}H_{37}F_3N_4O_{10}S$: 762.2. Found ($M+H^+$): 763.2.



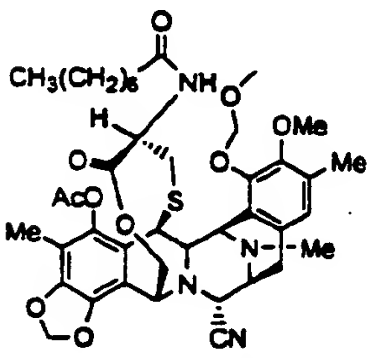
Compound **2l** (using succinic anhydride): ^1H NMR (300 MHz, $CDCl_3$): δ 6.79 (s, 1H), 6.04 (dd, 2H), 5.63 (bd, 1H), 5.18 (dd, 2H), 5.02 (d, 1H), 4.59-4.53 (m, 2H), 4.35 (d, 1H), 4.28 (s, 1H), 4.21-4.17 (m, 2H), 3.76 (s, 3H), 3.57 (s, 3H), 3.54-3.44 (m, 2H), 2.92 (bd, 2H), 2.69-2.63 (m, 2H), 2.53-2.48 (m, 2H), 2.38-2.07 (m, 2H), 2.28 (s, 6H), 2.18 (s, 3H), 2.02 (s, 3H); ESI-MS m/z: Calcd. for $C_{37}H_{42}N_4O_{12}S$: 766.2. Found ($M+H^+$): 767.3.



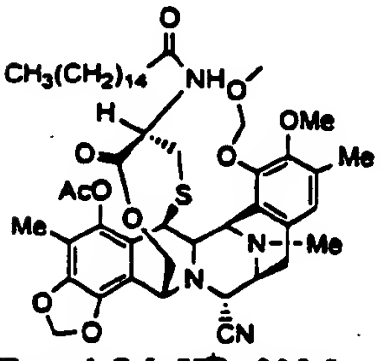
Compound 25 (from Compound 23 using 1 equiv of Ac_2O as the anhydride): ^1H NMR (300 MHz, $CDCl_3$): δ 6.59 (s, 1H), 5.97 (dd, 2H), 5.87 (s, 1H), 5.53 (s, 1H), 5.51 (d, 1H), 5.00 (d, 1H), 4.62-4.58 (m, 1H), 4.44 (s 1H), 4.31 (s, 1H), 4.29 (d, 1H), 4.16 (d, 1H), 4.09 (dd, 1H), 3.79 (s, 3H), 3.54-3.52 (m, 1H), 3.44-3.42 (m, 1H), 2.93-2.91 (m, 2H), 2.46 (dd, 1H), 2.33 (s, 3H), 2.23 (dd, 1H), 2.15 (s, 3H), 2.14 (s, 3H), 1.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 169.0, 148.3, 146.4, 146.0, 143.0, 136.4, 130.7, 129.2, 120.4, 119.0, 118.1, 112.4, 112.3, 107.8, 101.4, 61.1, 60.5, 59.2, 58.8, 54.7, 54.5, 51.6, 43.3, 41.4, 31.4, 23.8, 22.9, 16.2, 8.7; ESI-MS m/z: Calcd. for $C_{31}H_{34}N_4O_8S$: 580.2. Found ($M+H^+$): 581.3.

Example 2

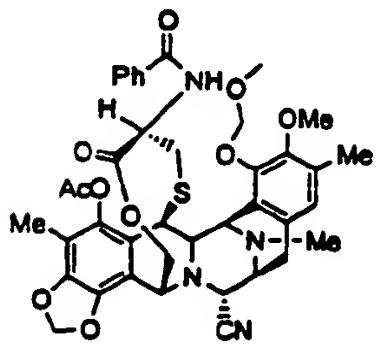
Method B: To a solution of 1 equiv. of **1** (**2p** for **2t** and **9**, and **11** for **13e-f**) and 1.5 equiv. of acid coevaporated twice with anhydrous toluene in CH_2Cl_2 (0.05M) under Argon, were added 2 equiv. of DMAP and 2 equiv. of EDC·HCl. The reaction was stirred for 3h 30 min. After this time was diluted with CH_2Cl_2, washed with brine and the organic layer dried with Na_2SO_4. Flash chromatography gives pure compounds.



Compound **2e** (using $CH_3(CH_2)_6CO_2H$ as the acid): ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.04 (dd, 2H), 5.50 (bd, 1H), 5.18 (dd, 2H), 5.02 (d, 1H), 4.60 (ddd, 1H), 4.53 (bp, 1H), 4.35 (d, 1H), 4.28 (s, 1H), 4.19 (d, 1H), 4.18 (dd, 1H), 3.76 (s, 3H), 3.58 (s, 3H), 3.48-3.43 (m, 2H), 2.93 (bd, 2H), 2.29-1.99 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H), 1.31-1.23 (m, 10H), 0.89 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 170.6, 168.4, 149.6, 148.5, 145.8, 141.0, 140.4, 130.9, 130.5, 125.7, 124.5, 120.4, 117.9, 113.4, 102.0, 99.2, 61.5, 60.2, 59.6, 59.3, 58.7, 57.5, 55.0, 54.5, 51.9, 41.8, 41.4, 36.4, 32.7, 31.7, 29.3, 29.1, 25.4, 23.7, 22.6, 20.3, 16.1, 14.0, 9.6; ESI-MS m/z: Calcd. for $C_{41}H_{52}N_4O_{10}S$: 792.3. Found ($M+H^+$): 793.3.

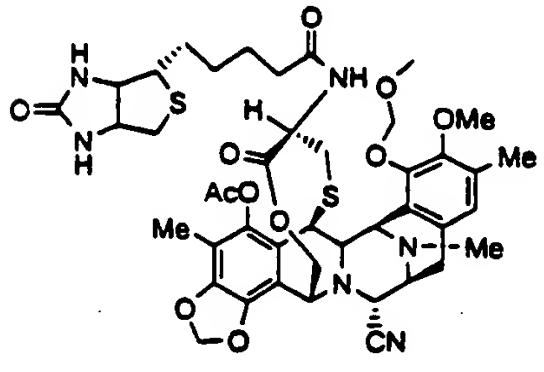


Compound **2f** (using $CH_3(CH_2)_{14}CO_2H$ as the acid): ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.05 (dd, 2H), 5.50 (bd, 1H), 5.18 (dd, 2H), 5.02 (d, 1H), 4.60 (ddd, 1H), 4.56-4.50 (bp, 1H), 4.35 (d, 1H), 4.28 (bs, 1H), 4.20 (d, 1H), 4.18 (dd, 1H), 3.76 (s, 3H), 3.57 (s, 3H), 3.54-3.44 (m, 2H), 2.93-2.92 (bd, 2H), 2.37-2.01 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H), 2.03 (s, 3H), 1.60-1.56 (m, 2H), 1.40-1.20 (m, 24H), 0.88 (t, 3H); ESI-MS m/z: Calcd. for $C_{49}H_{68}N_4O_{10}S$: 904.5. Found ($M+H^+$): 905.5.

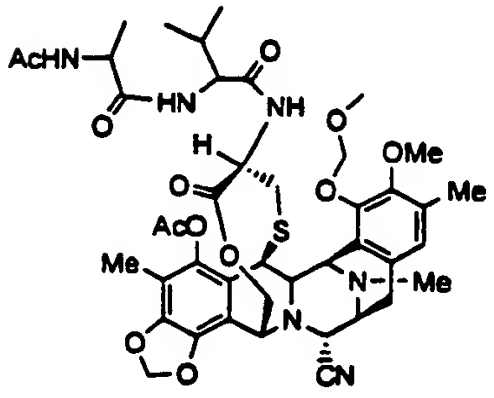


Compound **2g** (using $PhCO_2H$ as the acid): ^1H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H), 7.57-7.46 (m, 3H), 6.69 (s, 1H), 6.35 (d, 1H), 6.06 (dd, 2H), 5.14 (dd, 2H), 5.07 (d, 1H), 4.76 (dt, 1H), 4.58 (bp, 1H), 4.36-4.33 (m, 2H), 4.24-

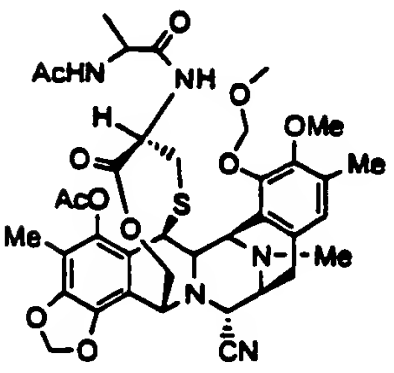
4.18 (m, 2H), 3.62 (s, 3H), 3.55 (s, 3H), 3.49-3.46 (m, 2H), 2.94 (bd, 2H), 2.62-2.55 (m, 1H), 2.28-1.93 (m, 1H), 2.28 (s, 3H), 2.16 (s, 3H), 2.04 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 168.4, 166.4, 149.3, 148.4, 145.9, 141.1, 140.6, 134.5, 134.2, 131.6, 131.4, 130.5, 128.6, 126.9, 125.2, 124.5, 120.7, 118.0, 113.4, 102.0, 99.2, 61.6, 60.2, 59.8, 59.2, 58.6, 57.4, 55.0, 54.6, 53.2, 41.9, 41.4, 32.9, 23.9, 20.2, 15.7, 9.6; ESI-MS m/z: Calcd. for $C_{40}H_{42}N_4O_{10}S$: 770.3. Found ($M+H^+$): 771.3.



Compound **2k** (using (+)-biotin as the acid): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (s, 1H), 6.04 (dd, 2H), 6.00 (s, 1H), 5.80 (s, 1H), 5.39 (bd, 1H), 5.18 (dd, 3H), 4.78 (d, 1H), 4.64-4.51 (m, 3H), 4.34-4.28 (m, 3H), 4.19 (dd, 1H), 3.77 (s, 3H), 3.57 (s, 3H), 3.47-3.39 (m, 2H), 3.19-3.13 (m, 1H), 3.02-2.74 (m, 4H), 2.28-1.47 (m, 10H), 2.28 (s, 6H), 2.14 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 171.3, 165.6, 163.7, 149.6, 148.4, 145.9, 141.0, 140.5, 131.1, 130.7, 125.8, 124.8, 120.2, 118.4, 113.7, 113.3, 102.0, 99.1, 61.5, 61.4, 61.3, 60.0, 59.6, 59.3, 58.4, 57.4, 56.1, 55.2, 54.6, 51.8, 42.2, 41.3, 41.1, 35.2, 32.1, 28.2, 28.1, 25.4, 24.0, 20.3, 16.1, 9.5; ESI-MS m/z: Calcd. for $C_{43}H_{52}N_6O_{11}S_2$: 892.3. Found ($M+H^+$): 894.1.

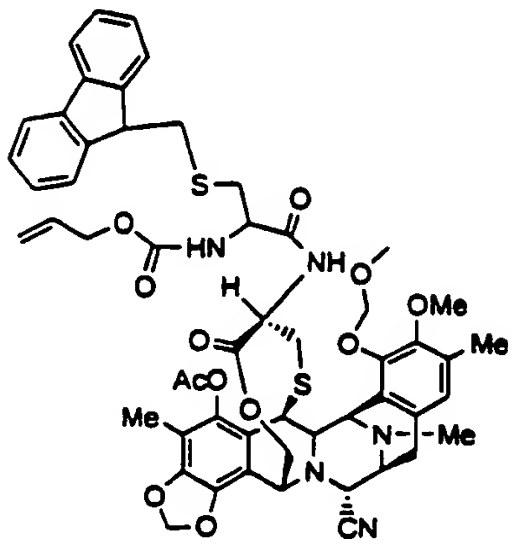


Compound **2t** (from Compound **2p** using Ac-L-alanine as the acid): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.60-6.56 (m, 1H), 6.26 (bt, 1H), 6.04 (dd, 2H), 5.58 (bt, 1H), 5.17 (dd, 2H), 5.00 (d, 1H), 4.64-4.60 (m, 1H), 4.56 (bp, 1H), 4.48 (dt, 1H), 4.35 (d, 1H), 4.29 (s, 1H), 4.20-4.14 (m, 2H), 4.12-4.05 (m, 1H), 3.75, 3.76 (2s, 3H), 3.56 (s, 3H), 3.47-3.42 (m, 2H), 2.98-2.89 (m, 2H), 2.42-1.98 (m, 3H), 2.42 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.36, 1.33 (2d, 3H), 1.06, 1.03 (2d, 3H), 0.94, 0.93 (2d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 170.2, 169.6, 169.7, 168.5, 149.6, 148.6, 145.9, 141.1, 140.5, 131.8, 130.3, 125.4, 124.4, 120.3, 117.9, 113.4, 102.0, 99.2, 61.5, 60.2, 59.6, 59.4, 59.3, 58.5, 57.8, 57.7, 57.4, 54.9, 54.5, 52.0, 51.9, 48.9, 48.8, 42.0, 41.3, 32.7, 32.2, 32.1, 23.8, 23.1, 23.1, 20.3, 19.2, 19.2, 19.1, 18.4, 17.7, 17.7, 16.2, 9.5. ESI-MS m/z: Calcd. for $C_{43}H_{54}N_6O_{12}S$: 878.3. Found ($M+H^+$): 879.2.

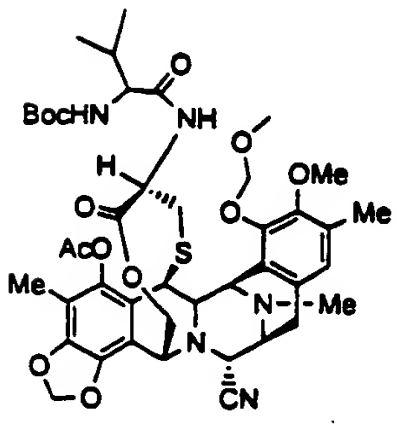


Compound **2w** (using Ac-L-alanine as the acid): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89, 6.77 (2s, 1H), 6.25 (dd, 1H), 6.05 (dd, 2H), 5.72, 5.55 (2bd, 1H), 5.22-5.13 (2dd, 2H), 5.02, 5.01 (2d, 1H), 4.60-4.18 (m, 7H), 3.77, 3.74 (2s, 3H), 3.56 (s, 3H), 3.48-3.43 (m, 2H), 2.93-2.91 (bd, 2H), 2.42-1.98 (m, 2H), 2.42, 2.37 (2s, 3H), 2.29, 2.28 (2s, 3H), 2.17, 2.15 (2s, 3H), 2.03 (s, 3H), 1.99, 1.97 (2s, 3H), 1.46, 1.22 (2d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 170.1, 169.9, 169.3, 169.2, 168.6, 149.8, 149.4, 148.7, 148.5, 145.9, 141.1, 140.5, 140.4, 132.0, 131.6, 130.6, 130.2, 125.5, 124.9, 124.4, 120.4, 120.2, 117.9, 113.6, 113.4, 102.0, 99.2, 61.6, 61.5, 60.4, 60.3, 59.6, 59.5, 59.4, 59.2, 58.8, 58.3, 57.5, 55.0, 55.0, 54.6, 52.2, 51.8, 48.6,

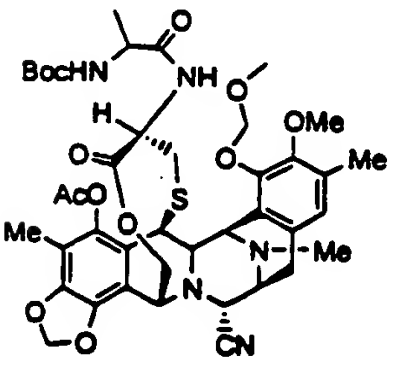
48.5, 42.1, 42.0, 41.4, 32.5, 32.4, 23.8, 23.7, 23.2, 23.2, 20.3, 19.9, 19.8, 16.0, 15.9, 9.6. ESI-MS m/z: Calcd. for $C_{38}H_{45}N_5O_{11}S$: 779.3. Found ($M+H^+$): 780.2.



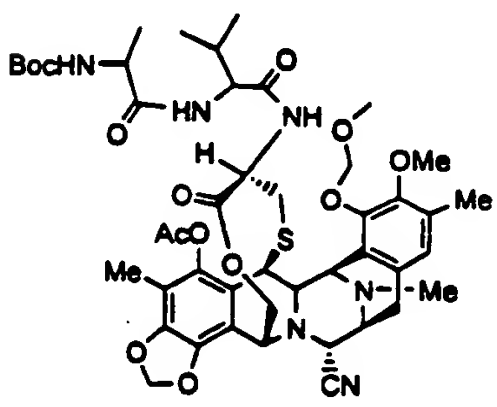
Compound **2y** (using $FmSCH_2CH(NHAlloc)CO_2H$ as the acid): ^1H NMR (300 MHz, $CDCl_3$): δ 7.77-7.67 (m, 4H), 7.42-7.26 (m, 4H), 6.75 (s, 1H), 6.12 (bd, 1H), 6.04 (dd, 2H), 5.97-5.88 (m, 1H), 5.53 (bd, 1H), 5.35-5.21 (m, 2H), 5.15 (dd, 2H), 4.99 (d, 1H), 4.61-4.55 (m, 4H), 4.34 (d, 1H), 4.30 (s, 1H), 4.20-4.17 (m, 4H), 3.70 (s, 3H), 3.54 (s, 3H), 3.46 (d, 1H), 3.45-3.40 (m, 1H), 3.21-3.14 (m, 1H), 3.04-2.83 (m, 5H), 2.41-2.03 (m, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H); ESI-MS m/z: Calcd. for $C_{54}H_{57}N_5O_{12}S_2$: 1031.3. Found (M^+): 1032.2.



Compound **7** (using Boc-L-valine as the acid): ^1H NMR (300 MHz, $CDCl_3$): δ 6.80 (s, 1H), 6.04 (dd, 2H), 5.86 (bd, 1H), 5.15 (dd, 2H), 5.02 (d, 1H), 4.98 (bd, 1H), 4.63-4.60 (m, 1H), 4.55 (bp, 1H), 4.35 (d, 1H), 4.30 (s, 1H), 4.22-4.16 (m, 2H), 3.83 (dd, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 3.48-3.42 (m, 2H), 2.93-2.90 (m, 2H), 2.41-2.03 (m, 3H), 2.41 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H), 1.46 (s, 9H), 1.01 (d, 3H), 0.87 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 168.5, 165.2, 155.3, 148.6, 145.9, 141.1, 140.5, 131.6, 130.4, 125.5, 124.5, 120.5, 118.0, 113.5, 113.4, 102.0, 99.2, 61.6, 60.0, 59.6, 59.3, 58.4, 57.5, 55.0, 54.6, 52.1, 42.0, 41.4, 32.7, 31.6, 28.3, 23.8, 20.2, 19.1, 17.5, 16.3, 9.6. ESI-MS m/z: Calcd. for $C_{43}H_{55}N_5O_{12}S$: 865.4. Found ($M+H^+$): 866.3.

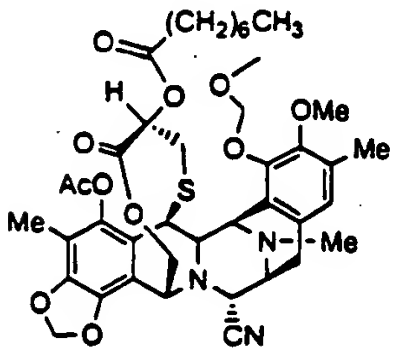


Compound **8** (using Boc-L-alanine as the acid): ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (s, 1H), 6.04 (dd, 2H), 5.86 (bp, 1H), 5.16 (dd, 2H), 5.03 (bp, 1H), 5.02 (d, 1H), 4.56-4.50 (m, 2H), 4.34 (d, 1H), 4.29 (s, 1H), 4.20-4.15 (m, 2H), 3.98-3.78 (m, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 3.47-3.43 (m, 2H), 2.91 (bd, 2H), 2.37-2.02 (m, 2H), 2.37 (s, 3H), 2.27 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 1.46 (s, 9H), 1.37 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 170.1, 168.4, 154.6, 149.5, 148.5, 145.8, 141.0, 140.4, 131.3, 130.4, 125.6, 124.4, 120.3, 117.9, 113.3, 101.9, 99.1, 61.4, 60.1, 59.6, 59.2, 58.5, 57.4, 54.9, 54.5, 52.1, 49.9, 41.8, 41.3, 32.4, 28.3, 23.8, 20.2, 19.5, 16.1, 9,5. ESI-MS m/z: Calcd. for $C_{41}H_{51}N_5O_{12}S$: 837.3. Found ($M+H^+$): 838.4.

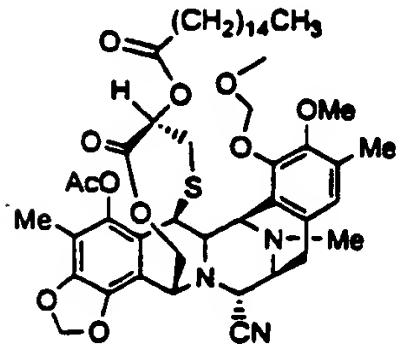


Compound **9** (using Boc-L-alanine as the acid): ^1H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.66 (bd, 1H), 6.04 (dd, 2H), 5.58 (bd, 1H), 5.17 (dd, 2H), 5.01 (d, 1H), 4.99 (bp, 1H), 4.66-4.63 (m, 1H), 4.56 (bp, 1H), 4.35 (d, 1H), 4.29 (s, 1H), 4.19-4.05 (m, 4H), 3.76 (s, 3H), 3.56 (s, 3H), 3.47-3.42 (m, 2H), 2.92-2.89 (m, 2H), 2.44-2.02 (m, 3H), 2.44 (s, 3H), 2.28 (s, 3H), 2.16 (s,

3H), 2.02 (s, 3H), 1.41 (s, 9H), 1.32 (d, 3H), 1.03 (d, 3H), 0.93 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 170.2, 169.7, 168.5, 149.7, 148.7, 145.9, 141.0, 140.5, 132.0, 130.2, 125.3, 124.4, 120.3, 117.9, 113.5, 102.0, 99.2, 61.5, 60.2, 59.6, 59.4, 58.5, 57.7, 57.4, 55.0, 54.6, 51.9, 50.2, 42.0, 41.4, 32.7, 32.2, 28.2, 23.8, 20.3, 19.1, 18.1, 17.8, 16.3, 9.6. ESI-MS m/z: Calcd. for $C_{46}H_{60}N_6O_{13}S$: 936.4. Found (M^+): 937.2.



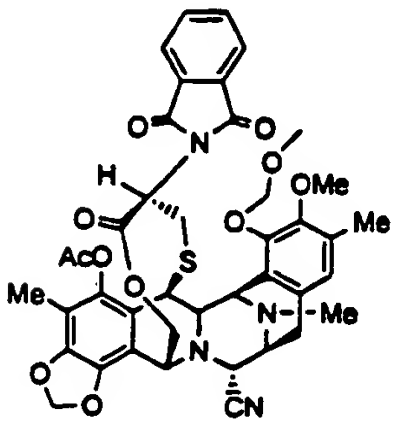
Compound **13e** (using 5 equiv. of $CH_3(CH_2)_6CO_2H$ as the acid, 7 equiv. of DMAP and 7 equiv. of EDC·HCl): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.04 (dd, 2H), 5.17 (dd, 2H), 5.02-4.98 (m, 2H), 4.56 (bp, 1H), 4.34 (d, 1H), 4.28 (s, 1H), 4.19 (d, 1H), 4.11 (dd, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 3.46 (d, 1H), 3.42-3.39 (m, 1H), 2.89-2.87 (m, 2H), 2.32-1.96 (m, 4H), 2.30 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H), 1.60-1.55 (m, 2H), 1.32-1.23 (m, 8H), 0.90 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 168.6, 167.1, 148.9, 148.2, 145.8, 141.1, 140.6, 130.7, 125.3, 125.1, 124.7, 120.9, 118.1, 113.6, 113.1, 102.0, 99.2, 71.4, 61.5, 60.0, 59.8, 59.2, 58.6, 57.4, 55.0, 54.6, 41.6, 41.5, 33.8, 31.7, 29.1, 28.9, 24.7, 23.9, 22.6, 20.2, 15.9, 14.0, 9.6. ESI-MS m/z: Calcd. for $C_{41}H_{51}N_3O_{11}S$: 793.3. Found ($M+H^+$): 794.9.



Compound **13f** (using 4 equiv. of $CH_3(CH_2)_{14}CO_2H$ as the acid, 6 equiv. of DMAP and 6 equiv. of EDC·HCl): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.04 (dd, 2H), 5.17 (dd, 2H), 5.02-4.98 (m, 2H), 4.56 (bp, 1H), 4.34 (d, 1H), 4.28 (s, 1H), 4.19 (d, 1H), 4.12 (dd, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 3.46 (d, 1H), 3.45-3.41 (m, 1H), 2.89-2.87 (m, 2H), 2.37-1.96 (m, 4H), 2.30 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H), 2.04 (s, 3H), 1.63-1.58 (m, 2H), 1.35-1.23 (m, 24H), 0.88 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 168.6, 167.1, 148.9, 148.2, 145.8, 141.1, 140.6, 130.7, 125.3, 125.1, 124.7, 120.9, 118.1, 113.6, 113.1, 102.0, 99.2, 71.4, 61.5, 60.0, 59.8, 59.2, 58.6, 57.4, 55.0, 54.6, 41.6, 41.5, 33.9, 31.9, 31.7, 30.9, 29.7, 29.5, 29.3, 29.3, 29.2, 29.1, 24.7, 23.9, 22.7, 20.2, 15.9, 14.1, 9.6.

Example 3

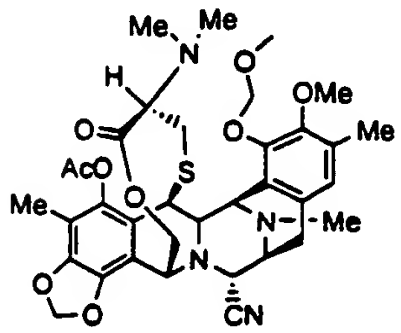
Method C: To a solution of 1 equiv. of 1 coevaporated twice with anhydrous toluene in CH_2Cl_2 (0.05M) under Argon, were added 1.05 equiv. of phthalic anhydride. After 30 min the reaction was cold to 0°C and 2.5 equiv. of Et_3N and 1.5 equiv. of $ClCO_2Et$ were added. 5 min later the reaction was warmed to RT and stirred for 7h. Then it was diluted with CH_2Cl_2, washed with a saturated solution of $NaHCO_3$ and the organic layer dried with Na_2SO_4. Flash chromatography (hex/EtOAc, 3:2) gives **2d** in 85% yield.



Compound **2j**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.70 (m, 4H), 6.67 (s, 1H), 6.06 (dd, 2H), 5.19 (dd, 2H), 5.05 (d, 1H), 4.64-4.62 (m, 2H), 4.37 (d, 1H), 4.32 (s, 1H), 4.20 (d, 1H), 4.12 (dd, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 3.50 (d, 1H), 3.41-3.40 (m, 1H), 2.85-2.83 (m, 2H), 2.36-2.11 (m, 2H), 2.33 (s, 3H), 2.31 (s, 3H), 2.14 (s, 3H), 2.05 (s, 3H); ESI- MS m/z: Calcd. for $C_{41}H_{40}N_4O_{11}S$: 796.2. Found ($M+H^+$): 797.2.

Example 4

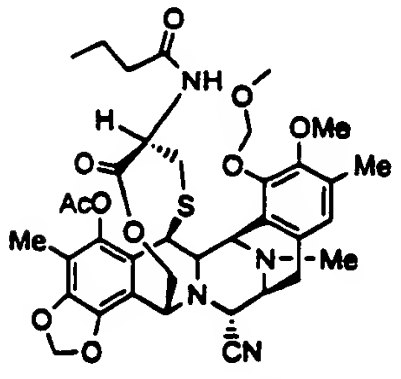
Method D: To a solution of 1 equiv. of 1 in CH_3CN/CH_2Cl_2 3:1 (0.025M) under Argon, were added 1 equiv. of formaline solution (37%) and 1 equiv. of $NaBH_3CN$. The solution was stirred at room temperature for 30 min. Then, 2 equiv. of acetic acid were added the solution which turned to orange-yellow was stirred for 1h 30 min. After this time the reaction mixture was diluted with CH_2Cl_2, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4. Flash chromatography gives the pure compound.



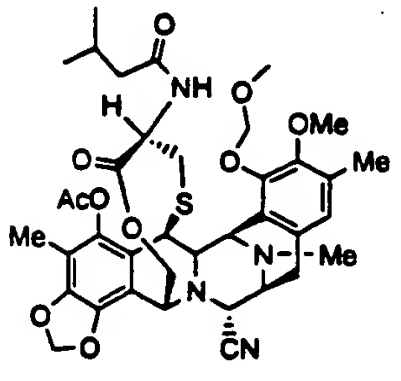
Compound **2m**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.66 (s, 1H), 6.03 (dd, 2H), 5.17 (dd, 2H), 4.98 (d, 1H), 4.58 (bp, 1H), 4.32 (d, 1H), 4.25 (s, 1H), 4.15-4.13 (m, 1H), 3.95 (dd, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 3.54-3.41 (m, 3H), 2.92-2.80 (m, 2H), 2.33 (s, 3H), 2.17 (s, 3H), 2.17-2.07 (bp, 6H), 2.16 (s, 3H), 2.04 (s, 3H), 1.86 (dd, 2H); ESI-MS m/z: Calcd. for $C_{35}H_{42}N_4O_9S$: 694.3. Found ($M+H^+$): 695.3.

Example 5

Method E: To a solution of 1 equiv. of **1** (**3p** for **3q-r**, **3s** for **3u**, **3v** for **3x**, **11** for **13c**, **13h**, **13ll** and **24** for **26**) in CH_2Cl_2 (0.08M) under Argon at RT were added 1.1 equiv. of pyridine. Then the reaction was cold to 0°C and 1.1 equiv of the acid chloride were added. 5 min later the reaction was warmed to RT and stirred for 45 min. Then it was diluted with CH_2Cl_2, washed with a saturated solution of NaCl and the organic layer dried with Na_2SO_4. Flash chromatography gives pure compounds.

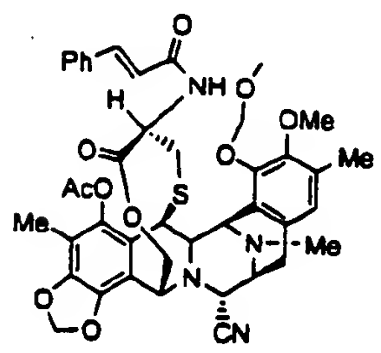


Compound **2c** (using butyryl chloride): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.04 (dd, 2H), 5.52 (bd, 1H), 5.17 (dd, 2H), 5.02 (d, 1H), 4.61 (ddd, 1H), 4.52 (bp, 1H), 4.34 (dd, 1H), 4.27 (s, 1H), 4.19 (d, 1H), 4.17 (dd, 1H), 3.75 (s, 3H), 3.56 (s, 3H), 3.47-3.43 (m, 2H), 2.92 (bd, 2H), 2.34-1.98 (m, 4H), 2.28 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.71-1.58 (m, 2H), 0.96 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 170.6, 168.4, 149.6, 148.5, 145.8, 141.0, 140.4, 131.0, 130.5, 125.7, 124.6, 120.4, 117.9, 113.4, 102.0, 99.1, 61.5, 60.1, 59.6, 59.2, 58.6, 57.4, 55.0, 54.5, 51.9, 41.8, 41.3, 38.2, 32.7, 23.7, 20.2, 18.8, 16.1, 13.7, 9.5. ESI-MS m/z: Calcd. for $C_{37}H_{44}N_4O_{10}S$: 736.3. Found ($M+H^+$): 737.2.

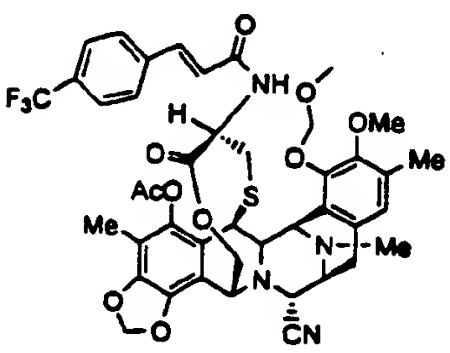


Compound **2d** (using isovaleryl chloride): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.76 (s, 1H), 6.05 (dd, 2H), 5.50 (bd, 1H), 5.17 (dd, 2H), 5.02 (d, 1H), 4.63 (ddd, 1H), 4.53 (bp, 1H), 4.35 (dd, 1H), 4.28 (s, 1H), 4.20 (d, 1H), 4.18 (dd, 1H), 3.76 (s, 3H), 3.56 (s, 3H), 3.47-3.43 (m, 2H), 2.92 (bd, 2H), 2.30-1.92 (m, 5H), 2.30 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H), 0.99 (d, 3H), 0.93 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 170.6, 168.4, 149.6, 148.5, 141.0, 140.5, 130.9,

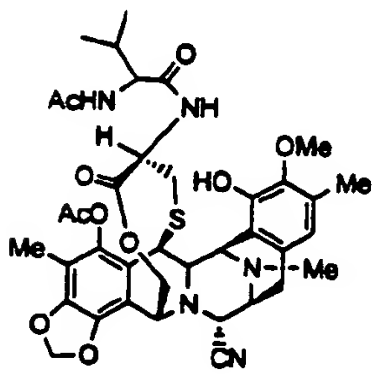
130.5, 125.7, 124.6, 120.4, 118.0, 113.5, 113.4, 102.0, 99.2, 61.5, 60.1, 59.6, 59.3, 58.6, 57.5, 55.0, 54.6, 51.8, 45.6, 41.9, 41.4, 31.8, 25.8, 23.8, 22.5, 22.4, 20.2, 16.3, 9.6. ESI-MS m/z: Calcd. for $C_{38}H_{46}N_4O_{10}S$: 750.3. Found ($M+H^+$): 751.3.



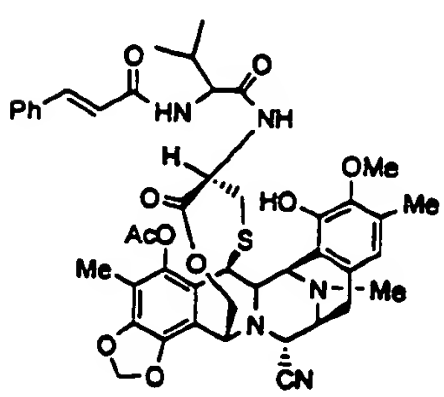
Compound **2h** (using cinnamoyl chloride): ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, 1H), 7.55-7.51 (m, 2H), 7.44-7.37 (m, 3H), 6.85 (s, 1H), 6.24 (d, 1H), 6.05 (dd, 2H), 5.72 (d, 1H), 5.16 (dd, 2H), 5.05 (d, 1H), 4.71 (ddd, 1H), 4.54 (bp, 1H), 4.35 (dd, 1H), 4.29 (s, 1H), 4.22-4.17 (m, 2H), 3.68 (s, 3H), 3.56 (s, 3H), 3.48-3.44 (m, 2H), 2.97-2.95 (m, 2H), 2.51-2.45 (m, 1H), 2.27-2.03 (m, 1H), 2.27 (s, 6H), 2.19 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 168.4, 164.5, 149.7, 148.5, 145.8, 142.1, 141.0, 140.4, 134.7, 131.1, 130.5, 129.8, 128.8, 127.9, 125.5, 124.4, 120.4, 119.7, 118.0, 113.4, 113.3, 102.0, 99.1, 61.4, 60.3, 59.6, 59.2, 58.8, 57.4, 54.9, 54.5, 52.6, 41.7, 41.4, 32.7, 23.8, 20.2, 16.3, 9.6. ESI-MS m/z: Calcd. for $C_{42}H_{44}N_4O_{10}S$: 796.3. Found ($M+H^+$): 797.2.



Compound **2i** (using trans-3-(trifluoromethyl)-cinnamoyl chloride): ^1H NMR (300 MHz, $CDCl_3$): δ 7.82-7.51 (m, 5H), 6.85 (s, 1H), 6.29 (d, 1H), 6.05 (dd, 2H), 5.75 (d, 1H), 5.17 (dd, 2H), 5.05 (d, 1H), 4.73-4.69 (m, 1H), 4.55 (bp, 1H), 4.36 (d, 1H), 4.39 (s, 1H), 4.23-4.18 (m, 2H), 3.69 (s, 3H), 3.57 (s, 3H), 3.48-3.44 (m, 2H), 2.96 (bd, 2H), 2.49-2.44 (m, 1H), 2.27-2.04 (m, 1H), 2.27 (s, 6H), 2.19 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 168.4, 163.8, 149.7, 148.5, 145.9, 141.1, 140.5, 135.5, 134.6, 131.6, 131.0, 130.6, 129.5, 126.3, 126.2, 125.6, 124.4, 123.7, 123.6, 121.5, 120.3, 117.9, 113.5, 113.3, 102.0, 99.2, 61.4, 60.4, 59.6, 59.2, 58.9, 57.5, 54.9, 54.5, 52.6, 41.8, 41.4, 32.6, 23.8, 20.3, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{43}H_{43}N_4F_3O_{10}S$: 864.3. Found ($M+H^+$): 865.0.

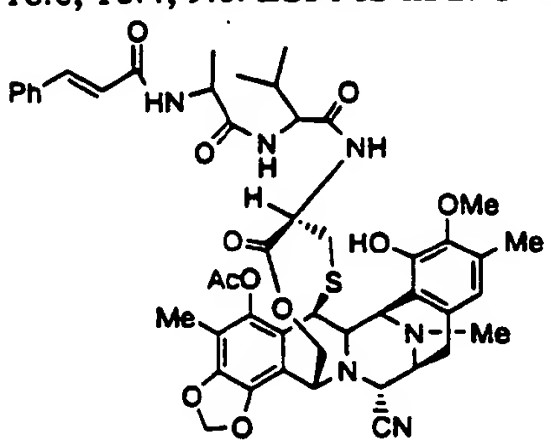


Compound **3q** (from Compound **3p** using acetyl chloride): ^1H NMR (300 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.08 (d, 1H), 6.05 (dd, 2H), 5.81 (s, 1H), 5.59 (d, 1H), 5.02 (d, 1H), 4.67 (dt, 1H), 4.58 (bp, 1H), 4.29 (s, 1H), 4.26 (dd, 1H), 4.21-4.16 (m, 1H), 4.09 (dd, 1H), 3.80 (s, 3H), 3.45-3.42 (m, 2H), 2.91-2.88 (m, 2H), 2.49 (s, 3H), 2.29-1.98 (m, 3H), 2.29 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.06 (d, 3H), 0.96 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 169.5, 168.6, 148.1, 145.9, 143.3, 141.1, 140.4, 130.4, 130.1, 120.4, 120.2, 118.5, 118.0, 113.5, 102.0, 61.4, 60.4, 59.3, 58.8, 57.7, 54.7, 54.6, 51.8, 42.0, 41.5, 32.7, 32.3, 23.8, 23.3, 20.5, 19.1, 18.0, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{38}H_{45}N_5O_{10}S$: 763.3. Found ($M+H^+$): 764.3

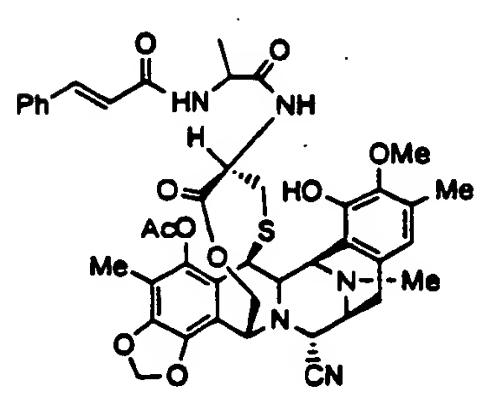


Compound **3r** (from Compound **3p** using cinnamoyl chloride): ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, 1H), 7.50-7.46 (m, 2H), 7.37-7.34 (m, 3H), 6.57 (s, 1H), 6.42 (d, 1H), 6.30 (d, 1H), 6.05 (dd, 2H), 5.81 (s, 1H), 5.64 (d,

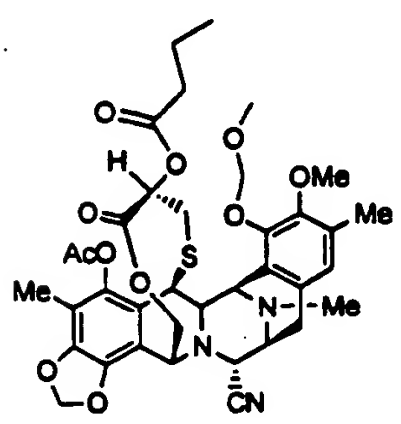
1H), 5.03 (d, 1H), 4.70-4.67 (m, 1H), 4.58 (bp, 1H), 4.30-4.24 (m, 3H), 4.21-4.17 (m, 2H), 3.82 (s, 3H), 3.45 (bd, 2H), 2.92-2.89 (m, 2H), 2.56 (s, 3H), 2.28-2.03 (m, 3H), 2.28 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H), 1.10 (d, 3H), 1.00 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 170.1, **169.4**, 168.5, 165.3, 148.1, 145.9, 143.4, 141.2, 140.4, 134.8, 130.5, 130.1, 129.7, 128.8, 127.8, 120.6, 120.4, 120.2, 118.5, 118.0, 113.5, 113.5, 102.0, 61.4, 60.4, 59.4, 58.9, 57.7, 54.7, 54.6, 51.9, 42.0, 41.5, 32.7, 23.8, 20.5, 19.2, 18.0, 16.4, 9.6. ESI-MS m/z: Calcd. for $C_{45}H_{49}N_5O_{10}S$: 851.3. Found ($M+H^+$): 852.3



Compound **3u** (from Compound 3s using cinnamoyl chloride): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 1H), 7.50-7.47 (m, 2H), 7.38-7.35 (m, 3H), 6.62 (d, 1H), 6.55 (s, 1H), 6.41 (d, 1H), 6.35 (d, 1H), 6.05 (dd, 2H), 5.82 (s, 1H), 5.60 (d, 1H), 5.02 (d, 1H), 4.68-4.60 (m, 2H), 4.58 (bp, 1H), 4.29 (s, 1H), 4.26 (dd, 1H), 4.21-4.15 (m, 2H), 4.10 (dd, 1H), 3.79 (s, 3H), 3.45-3.43 (m, 2H), 2.91-2.88 (m, 2H), 2.48 (s, 3H), 2.30-2.03 (m, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 1.41 (d, 3H), 1.04 (d, 3H), 0.94 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 170.2, 169.6, 168.5, 165.4, 148.0, 145.9, 143.3, 141.6, 141.1, 140.5, 134.7, 130.6, 129.8, 129.8, 128.8, 127.8, 120.3, 120.1, 118.7, 118.0, 113.5, 102.0, 61.5, 60.3, 59.4, 58.8, 57.8, 54.7, 54.6, 51.9, 49.0, 42.1, 41.5, 32.6, 32.3, 23.8, 20.5, 19.2, 18.6, 17.7, 16.3, 9.6. ESI-MS m/z: Calcd. for $C_{48}H_{54}N_6O_{11}S$: 922.4. Found ($M+H^+$): 923.1.

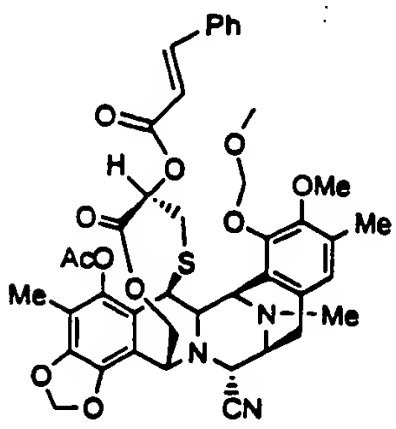


Compound **3x** (from Compound **3v** using cinnamoyl chloride): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, 1H), 7.49-7.46 (m, 2H), 7.37-7.34 (m, 3H), 6.59 (s, 1H), 6.48 (d, 1H), 6.39 (d, 1H), 6.05 (dd, 2H), 5.84 (s, 1H), 5.58 (d, 1H), 5.03 (d, 1H), 4.64-4.59 (m, 1H), 4.58 (bp, 1H), 4.36-4.8 (m, 1H), 4.28 (s, 1H), 4.26 (d, 1H), 4.22-4.17 (m, 2H), 3.81 (s, 3H), 3.45-3.43 (m, 2H), 2.92 (d, 2H), 2.53 (s, 3H), 2.28-2.03 (m, 2H), 2.28 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 1.54 (d, 3H);); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 170.1, 168.6, 164.9, 148.2, 145.9, 143.2, 141.1, 134.8, 130.5, 130.0, 129.7, 128.8, 127.8, 120.4, 120.4, 120.0, 118.8, 118.0, 113.6, 113.4, 102.0, 61.4, 60.6, 60.4, 59.3, 59.1, 54.8, 54.6, 51.7, 48.7, 41.9, 41.5, 32.5, 23.8, 20.5, 20.0, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{43}H_{45}N_5O_{10}S$: 823.3. Found ($M+H^+$): 824.3.

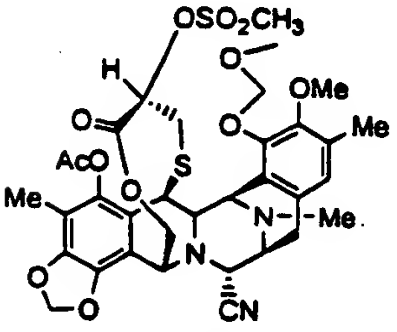


Compound **13c** (from Compound **11** using 20 equiv. of butyryl chloride and 30 equiv. of pyr): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.04 (dd, 2H), 5.17 (dd, 2H), 5.02 (bt, 1H), 5.01 (d, 1H), 4.57 (bp, 1H), 4.34 (dd, 1H), 4.29 (s, 1H), 4.19 (d, 1H), 4.12 (dd, 1H), 3.78 (s, 3H), 3.56 (s, 3H), 3.46 (d, 1H), 3.45-3.42 (m, 1H), 2.88 (bd, 2H), 2.30-2.16 (m, 3H), 2.30 (s, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 2.02-1.96 (m, 1H), 1.68-1.56 (m, 2H), 0.98 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 168.8, 167.3, 149.1, 148.4, 146.0, 141.3,

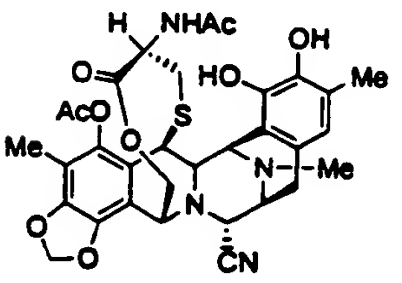
140.9, 131.0, 125.6, 125.0, 121.2, 118.3, 113.8, 113.3, 102.2, 99.4, 71.7, 61.7, 60.3, 60.0, 59.4, 58.8, 57.6, 55.2, 54.9, 41.9, 41.7, 36.1, 32.0, 24.2, 20.5, 18.5, 16.1, 13.9, 9.8. ESI-MS m/z: Calcd. for $C_{37}H_{43}N_3O_{11}S$: 737.3. Found ($M+Na^+$): 760.2.



Compound **13h** (from Compound **11** using 5 equiv. of cinnamoyl chloride, 7.5 equiv. of pyr and CH_3CN as cosolvent): ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, 1H), 7.56-7.53 (m, 2H), 7.43-7.39 (m, 3H), 6.72 (s, 1H), 6.30 (d, 1H), 6.05 (dd, 2H), 5.22-5.13 (m, 3H), 5.04 (d, 1H), 4.58 (bp, 1H), 4.35 (d, 1H), 4.31 (s, 1H), 4.21 (d, 1H), 4.15 (dd, 1H), 3.79 (s, 3H), 3.57 (s, 3H), 3.48 (d, 1H), 3.43-3.39 (m, 1H), 2.90-2.88 (m, 2H), 2.47-2.41 (m, 1H), 2.31 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 2.07-2.03 (m, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 167.1, 165.6, 148.8, 148.2, 145.7, 141.1, 140.6, 134.4, 130.9, 130.7, 130.4, 128.9, 128.2, 128.1, 125.2, 124.7, 120.9, 118.1, 117.3, 113.7, 113.1, 102.0, 99.2, 71.9, 61.5, 60.0, 59.8, 59.3, 58.5, 57.4, 54.9, 54.6, 41.7, 41.5, 31.8, 23.9, 20.2, 16.0, 9.6. ESI-MS m/z: Calcd. for $C_{42}H_{43}N_3O_{11}S$: 797.3. Found ($M+H^+$): 798.8.



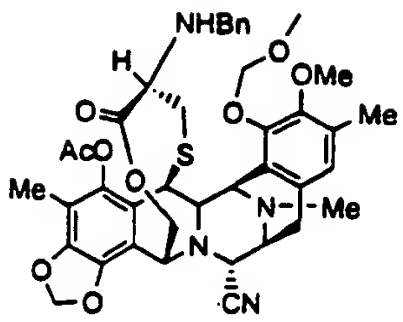
Compound **13ll** (from Compound **11** using 5 equiv. of methanesulfonyl chloride and 5 equiv. of Et_3N as base): ^1H NMR (300 MHz, $CDCl_3$): δ 6.65 (s, 1H), 6.04 (dd, 2H), 5.17 (dd, 2H), 5.00 (d, 1H), 4.93 (dd, 1H), 4.58 (bp, 1H), 4.34 (dd, 1H), 4.29 (s, 1H), 4.16-4.12 (m, 2H), 3.77 (s, 3H), 3.56 (s, 3H), 3.46 (d, 1H), 3.44-3.39 (m, 1H), 3.11 (s, 3H), 2.96-2.81 (m, 2H), 2.50-2.42 (m, 1H), 2.30 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H), 2.04-1.97 (m, 1H), 2.03 (s, 3H); ESI-MS m/z: Calcd. for $C_{34}H_{39}N_3O_{12}S_2$: 745.2. Found ($M+H^+$): 746.2.



Compound **26** (from Compound **24** using 1.05 equiv of acetyl chloride and without base): ^1H NMR (300 MHz, $CDCl_3$): δ 6.51 (s, 1H), 6.05 (d, 2H), 5.95 (s, 1H), 5.60 (d, 1H), 5.59 (bp, 1H), 5.03 (d, 1H), 4.58-4.53 (m, 2H), 4.27 (s, 1H), 4.26 (d, 1H), 4.20- 4.16 (m, 2H), 3.43-3.42 (m, 2H), 2.90-2.88 (m, 2H), 2.27-2.11 (m, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 169.5, 168.9, 145.8, 144.5, 140.9, 140.4, 139.9, 127.1, 123.6, 120.1, 119.8, 119.2, 118.1, 113.5, 113.4, 102.0, 61.3, 60.4, 59.2, 58.9, 54.7, 54.5, 52.0, 41.7, 41.4, 32.3, 23.5, 22.8, 20.6, 16.2, 9.6; ESI-MS m/z: Calcd. for $C_{32}H_{34}N_4O_9S$: 650.2. Found ($M+H^+$): 651.3.

Example 6

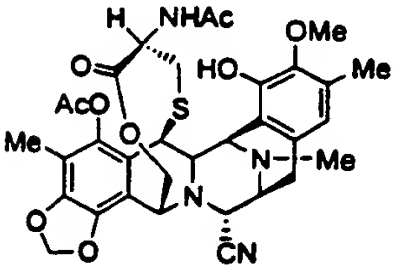
Method F: To a solution of 1 equiv. of **1** in DMF (0.03M) under Argon at room temperature, were added 0.9 equiv. of Cs_2CO_3 and 0.9 equiv on BnBr. After 2h 30 min the reaction was quenched with 1μL of AcOH, diluted with Hex/EtOAc (1:3), washed with H_2O and extracted with Hex/EtOAc (1:3). The organic layer was dried with Na_2SO_4. Flash chromatography give pure compound **2n**.



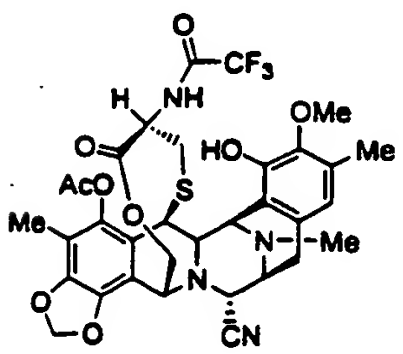
Compound **2n**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.20 (m, 5H), 6.56 (s, 1H), 6.02 (dd, 2H), 5.15 (dd, 2H), 5.04 (d, 1H), 4.51 (bp, 1H), 4.32 (d, 1H), 4.25-4.23 (m, 2H), 4.12 (dd, 1H), 3.74 (s, 3H), 3.62 (dd, 2H), 3.56 (s, 3H), 3.44-3.40 (m, 2H), 3.38-3.20 (m, 1H), 3.19-2.84 (m, 2H), 2.36-1.91 (m, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 2.03 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 168.6, 149.3, 148.2, 145.6, 140.9, 140.4, 139.9, 131.5, 130.3, 128.3, 128.1, 126.9, 124.9, 124.7, 120.9, 118.1, 113.8, 113.2, 101.9, 99.1, 61.5, 59.7, 59.6, 59.5, 59.2, 58.9, 57.4, 54.9, 54.7, 51.3, 41.5, 41.4, 33.3, 23.8, 20.3, 15.3, 9.6. ESI-MS m/z: Calcd. for $C_{40}H_{44}N_4O_9S$: 756.3. Found ($M+Na^+$): 779.2.

Example 7

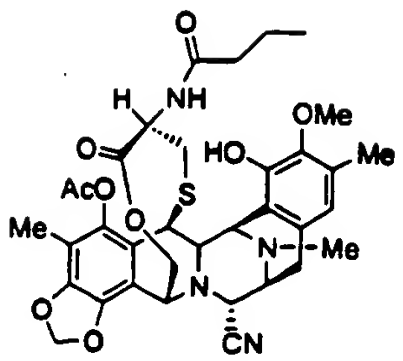
Method G: To a solution of 1 equiv. of **2a-n, 2t, 2w, 2y, 11, 12*, 13a-c, 13e-f, 13h, 13ll, 14a*** or **7-9** in CH_3CN/CH_2Cl_2 5:4 (0.026M) under Argon were added 6 equiv. of NaI and 6 equiv. of fresh distilled TMSCl. After 20 min the reaction was quenched with a saturated solution of $Na_2S_2O_4$, diluted with CH_2Cl_2, washed with $Na_2S_2O_4$ (x3), or with NaCl. The aqueous layer extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4. Flash chromatography gives pure compounds **3a-n, 3p, 3s-t, 3v-w, 3y-z, 15, 16*, 17a-c, 17e-f, 17h, 17ll, 18a***.



Compound **3a** (from **2a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.04 (dd, 2H), 5.78 (s, 1H), 5.52 (bd, 1H), 5.02 (d, 1H), 4.58 (ddd, 1H), 4.53 (bs, 1H), 4.27-4.25 (m, 2H), 4.19-4.15 (m, 2H), 3.77 (s, 3H), 3.44-3.43 (m, 2H), 2.92-2.90 (m, 2H), 2.36-2.02 (m, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 168.8, 168.4, 148.1, 145.8, 143.1, 141.0, 140.3, 130.7, 129.9, 129.0, 120.3, 119.0, 117.9, 113.5, 102.0, 61.3, 60.3, 60.2, 59.3, 58.9, 54.7, 54.5, 51.9, 41.8, 41.4, 32.4, 23.7, 22.8, 20.4, 16.0, 9.5; ESI-MS m/z: Calcd. for $C_{33}H_{36}N_4O_9S$: 664.2. Found ($M+H^+$): 665.2.

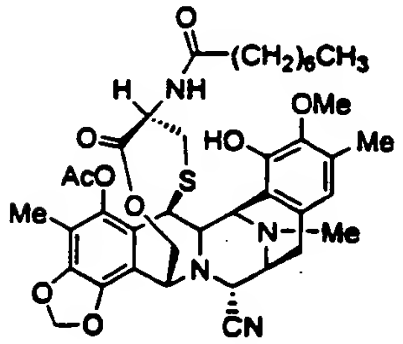


Compound **3b** (from **2b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 (s, 1H), 6.41 (bd, 1H), 6.05 (dd, 2H), 5.72 (s, 1H), 5.05 (d, 1H), 4.60 (bp, 1H), 4.54-4.51 (m, 1H), 4.32 (s, 1H), 4.26-4.18 (m, 3H), 3.74 (s, 3H), 3.46-3.42 (m, 2H), 2.97-2.80 (m, 2H), 2.44-2.38 (m, 1H), 2.30-2.03 (m, 1H), 2.30 (s, 3H), 2.27 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 168.5, 156.3, 155.8, 155.3, 147.6, 146.0, 143.1, 141.2, 140.5, 130.5, 129.9, 120.7, 120.6, 120.1, 118.0, 117.9, 113.2, 101.1, 61.4, 60.7, 60.1, 59.5, 58.9, 54.6, 54.5, 52.8, 42.0, 41.5, 31.9, 23.8, 20.4, 15.6, 9.6; ESI-MS m/z: Calcd. for $C_{33}H_{33}F_3N_4O_9S$: 718.2. Found ($M+H^+$): 719.2.

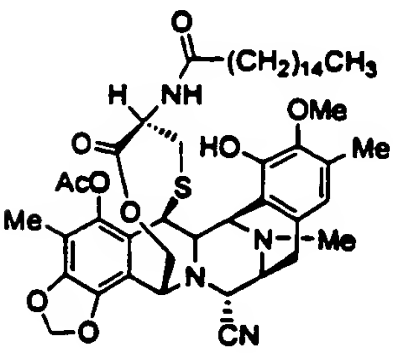


Compound **3c** (from **2c**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.03 (dd, 2H), 5.82 (s, 1H), 5.49 (bd, 1H), 5.02 (d, 1H), 4.61 (ddd, 1H), 4.53 (bp, 1H), 4.27-4.24 (m, 2H), 4.19-4.15 (m, 2H), 3.76 (s, 3H), 3.44-3.41 (m, 2H), 2.90 (bd, 2H), 2.31-1.94 (m, 4H), 2.31 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 1.67-1.57 (m, 2H), 0.95 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 170.5, 148.0, 145.8, 143.1, 141.0, 140.4, 130.8, 129.0, 120.4, 120.2, 119.0, 118.0, 113.4, 102.0, 61.4, 60.2, 59.4, 58.9, 54.7, 54.5, 51.7, 41.8, 41.4, 38.2, 32.6, 23.8, 20.5, 18.8, 16.0, 13.7, 9.6. ESI-MS m/z: Calcd. for $C_{35}H_{40}N_4O_9S$: 692.2. Found ($M+H^+$): 693.9.

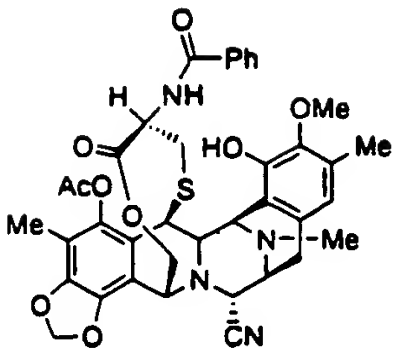
Compound **3d** (from **2d**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.04 (dd, 2H), 5.76 (s, 1H), 5.48 (bd, 1H), 5.02 (d, 1H), 4.66-4.60 (m, 1H), 4.53 (bp, 1H), 4.27-4.23 (m, 2H), 4.19-4.15 (m, 2H), 3.76 (s, 3H), 3.44-3.42 (m, 2H), 2.90 (bd, 2H), 2.33-1.90 (m, 5H), 2.33 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 0.98 (d, 3H), 0.92 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 170.6, 168.5, 148.0, 145.8, 143.1, 141.1, 140.4, 130.8, 129.0, 127.6, 120.5, 120.3, 119.1, 118.0, 113.5, 102.0, 74.2, 61.4, 60.3, 59.4, 58.8, 54.7, 54.6, 51.7, 45.5, 41.9, 41.5, 32.7, 25.8, 23.8, 22.5, 22.4, 20.5, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{36}H_{42}N_4O_9S$: 706.3. Found ($M+Na^+$): 729.2.



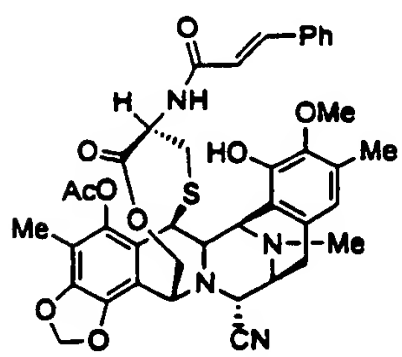
Compound **3e** (from **2e**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.04 (dd, 2H), 5.75 (s, 1H), 5.48 (bd, 1H), 5.02 (d, 1H), 4.60 (ddd, 1H), 4.53 (bp, 1H), 4.27-4.24 (m, 2H), 4.19-4.15 (m, 2H), 3.77 (s, 3H), 3.48-3.42 (m, 2H), 2.91 (bd, 2H), 2.32-1.97 (m, 4H), 2.32 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.62-1.41 (m, 2H), 1.390-1.25 (m, 8H), 0.89 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 170.6, 168.4, 148.0, 145.8, 143.1, 141.0, 140.4, 130.8, 129.0, 120.4, 120.2, 119.0, 118.0, 113.7, 113.5, 102.0, 61.4, 60.3, 59.4, 58.9, 54.7, 54.6, 51.8, 41.8, 41.5, 36.3, 32.6, 31.7, 29.3, 29.1, 25.4, 23.8, 22.6, 20.5, 16.1, 14.0, 9.6; ESI-MS m/z: Calcd. for $C_{39}H_{48}N_4O_9S$: 748.3. Found ($M+H^+$): 749.3.



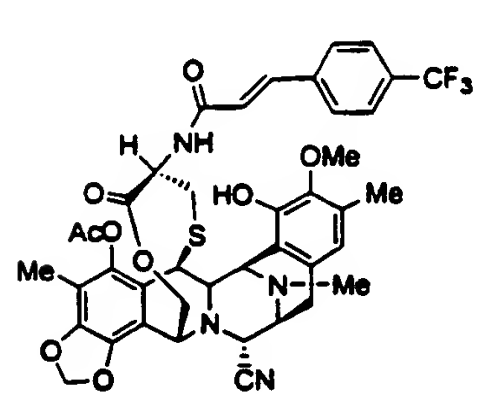
Compound **3f** (from **2f**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55 (s, 1H), 6.04 (dd, 2H), 5.73 (s, 1H), 5.48 (bd, 1H), 5.02 (d, 1H), 4.60 (ddd, 1H), 4.56-4.50 (bp, 1H), 4.28-4.24 (m, 2H), 4.20-4.14 (m, 2H), 3.77 (s, 3H), 3.44-3.40 (m, 2H), 2.92-2.90 (bd, 2H), 2.35-1.95 (m, 4H), 2.32 (s, 3H), 2.29 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 1.62-1.58 (m, 2H), 1.38-1.20 (m, 24H), 0.88 (t, 3H); ESI-MS m/z: Calcd. for $C_{47}H_{64}N_4O_9S$: 860.4. Found ($M+H^+$): 861.5.



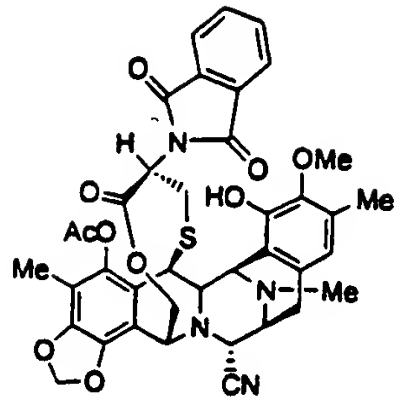
Compound **3g** (from **2g**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H), 7.57-7.45 (m, 3H), 6.48 (s, 1H), 6.35 (d, 1H), 6.06 (dd, 2H), 5.70 (s, 1H), 5.07 (d, 1H), 4.78-4.74 (m, 1H), 4.58 (bp, 1H), 4.33 (s, 1H), 4.26-4.18 (m, 3H), 3.61 (s, 3H), 3.47-3.45 (m, 2H), 2.92 (bd, 2H), 2.60-2.53 (m, 1H), 2.28-1.93 (m, 1H), 2.28 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 170.5, 166.4, 147.7, 145.9, 143.0, 141.1, 140.5, 134.2, 131.6, 130.8, 129.4, 128.6, 127.0, 120.4, 118.5, 118.0, 113.7, 113.4, 102.0, 61.5, 60.3, 60.1, 59.7, 58.8, 54.7, 53.1, 41.9, 41.5, 32.8, 23.9, 20.4, 15.6, 9.6; ESI-MS m/z: Calcd. for $C_{38}H_{38}N_4O_9S$: 726.2. Found ($M+H^+$): 727.2.



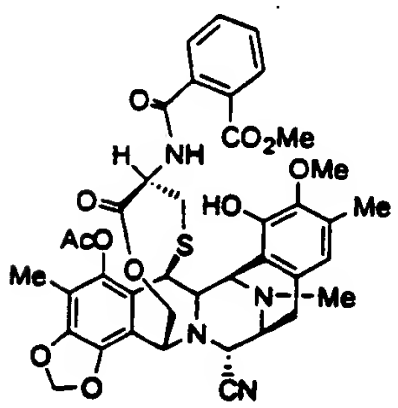
Compound **3h** (from **2h**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, 1H), 7.54-7.51 (m, 2H), 7.44-7.38 (m, 3H), 6.63 (s, 1H), 6.22 (d, 1H), 6.05 (dd, 2H), 5.79 (s, 1H), 5.73 (d, 1H), 5.05 (d, 1H), 4.71 (ddd, 1H), 4.55 (bp, 1H), 4.29 (s, 1H), 4.26 (s, 1H), 4.21-4.17 (m, 2H), 3.68 (s, 3H), 3.48-3.42 (m, 2H), 2.95-2.93 (m, 2H), 2.49-2.44 (m, 1H), 2.29-2.03 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 168.4, 164.5, 148.1, 145.8, 143.1, 142.0, 141.0, 140.4, 134.7, 130.8, 129.8, 129.2, 128.8, 127.9, 120.2, 119.8, 118.9, 118.0, 113.6, 113.3, 102.0, 61.4, 60.4, 60.2, 59.4, 59.0, 54.6, 54.6, 52.5, 41.8, 41.5, 32.6, 23.8, 20.5, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{40}H_{40}N_4O_9S$: 752.2. Found ($M+Na^+$): 775.8.



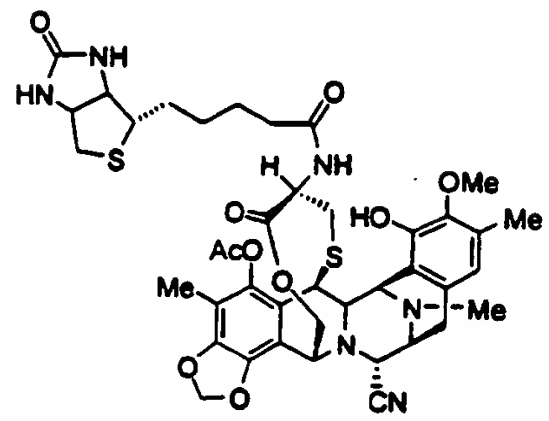
Compound **3i** (from **2i**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.66-7.51 (m, 4H), 6.64 (s, 1H), 6.26 (d, 1H), 6.05 (dd, 2H), 5.77 (s, 1H), 5.74 (d, 1H), 5.05 (d, 1H), 4.72 (ddd, 1H), 4.56 (bp, 1H), 4.29 (s, 1H), 4.26 (dd, 1H), 4.22-4.16 (m, 2H), 3.70 (s, 3H), 3.46-3.44 (m, 2H), 2.94 (bd, 2H), 2.47-2.40 (m, 1H), 2.30-2.03 (m, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 163.9, 148.1, 143.1, 141.1, 140.4, 135.6, 131.7, 130.9, 129.5, 129.0, 126.2, 123.6, 121.7, 120.3, 118.0, 113.3, 102.0, 99.2, 61.4, 60.5, 60.2, 59.4, 59.1, 54.7, 54.6, 52.5, 41.8, 41.5, 32.6, 23.8, 20.5, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{41}H_{39}N_4F_3O_9S$: 820.2. Found ($M+H^+$): 821.3.



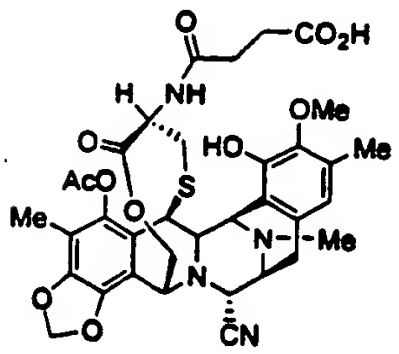
Compound **3j** (from **2j**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.68 (m, 4H), 6.26 (s, 1H), 6.06 (dd, 2H), 5.77 (s, 1H), 4.98 (d, 1H), 4.61-4.55 (m, 2H), 4.33-4.21 (m, 2H), 4.09 (d, 1H), 4.97 (dd, 1H), 3.97 (s, 3H), 3.47-3.31 (m, 2H), 2.93-2.77 (m, 2H), 2.36 (s, 3H), 2.33-2.14 (m, 2H), 2.23 (s, 3H), 2.17 (s, 3H), 2.05 (s, 3H); ESI-MS m/z: Calcd. for $C_{39}H_{36}N_4O_{10}S$: 752.2. Found ($M+H^+$): 753.2.



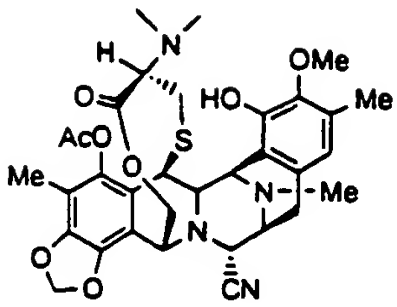
Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (dd, 1H), 7.66-7.45 (m, 3H), 6.13 (s, 1H), 6.07 (dd, 2H), 5.88 (d, 1H), 5.64 (s, 1H), 5.06 (d, 1H), 4.83-4.81 (m, 1H), 4.53 (bp, 1H), 4.30-4.17 (m, 4H), 3.79 (s, 3H), 3.61 (s, 3H), 3.45-3.40 (m, 2H), 2.94-2.85 (m, 2H), 2.29-2.04 (m, 2H), 2.29 (s, 3H), 2.14 (s, 3H), 2.04 (s, 6H); ESI-MS m/z: Calcd. for $C_{40}H_{40}N_4O_{11}S$: 784.2. Found ($M+H^+$): 785.1.



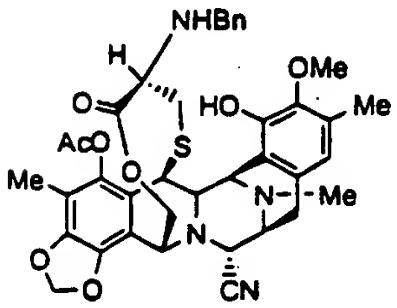
Compound **3k** (from **2k**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (s, 1H), 6.55 (s, 1H), 6.45 (s, 1H), 6.04 (dd, 2H), 5.38 (bd, 1H), 5.29 (bs, 1H), 5.15 (d, 1H), 4.66 (m, 1H), 4.60 (bp, 1H), 4.55-4.51 (m, 1H), 4.40 (d, 1H), 4.34-4.29 (m, 2H), 4.25 (s, 1H), 4.14 (d, 1H), 3.79 (s, 3H), 3.43-3.39 (m, 2H), 3.09-3.05 (m, 1H), 2.96-2.90 (m, 3H), 2.70 (d, 1H), 2.34-1.94 (m, 4H), 2.34 (s, 3H), 2.30 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 1.81-1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 170.8, 168.7, 163.8, 148.8, 145.8, 142.8, 141.1, 140.3, 131.2, 128.9, 120.7, 120.3, 120.1, 118.3, 113.5, 102.0, 61.9, 61.2, 60.2, 59.8, 59.4, 59.4, 56.4, 55.1, 54.7, 51.3, 41.8, 41.4, 41.1, 34.5, 32.6, 27.8, 27.7, 25.0, 24.1, 20.7, 16.1, 9.6; ESI-MS m/z: Calcd. for $C_{41}H_{48}N_6O_{10}S_2$: 849.0. Found ($M+H^+$): 850.0.



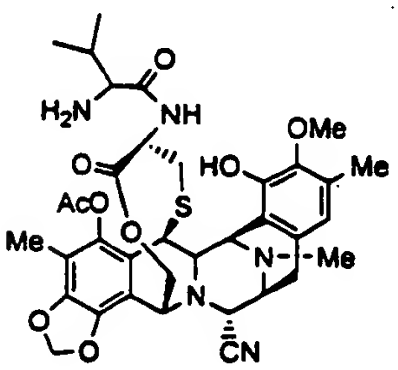
Compound **3l** (from **2l**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (s, 1H), 6.04 (dd, 2H), 5.90 (bp, 1H), 5.63 (bd, 1H), 5.02 (d, 1H), 4.60-4.55 (m, 2H), 4.27-4.17 (m, 4H), 3.76 (s, 3H), 3.47-3.39 (m, 2H), 2.90 (bd, 2H), 2.68-2.61 (m, 2H), 2.58-2.02 (m, 4H), 2.32 (s, 3H), 2.29 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 170.5, 170.2, 168.6, 148.1, 145.8, 143.1, 141.0, 140.3, 130.7, 129.2, 120.3, 120.0, 119.0, 118.0, 113.5, 113.3, 102.0, 61.3, 60.4, 60.3, 59.2, 58.9, 54.6, 54.4, 51.9, 41.8, 41.4, 32.3, **30.2**, 29.6, 29.1, **28.3**, 23.7, 20.5, 16.0, 9.6. ESI-MS m/z: Calcd. for $C_{35}H_{38}N_4O_{11}S$: 722.2. Found ($M+H^+$): 723.2.



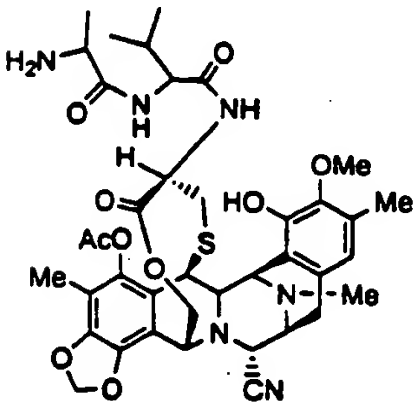
Compound **3m** (from **2m**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (s, 1H), 6.02 (d, 2H), 5.67 (s, 1H), 4.98 (d, 1H), 4.55 (bp, 1H), 4.27-4.22 (m, 2H), 4.14 (d, 1H), 3.94 (dd, 1H), 3.78 (s, 3H), 3.65-3.38 (m, 3H), 2.96-2.79 (m, 2H), 2.44-2.02 (m, 7H), 2.34 (s, 3H), 2.20 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 1.88-1.82 (m, 1H); ESI-MS m/z: Calcd. for $C_{33}H_{38}N_4O_8S$: 650.2. Found ($M+H^+$): 651.3.



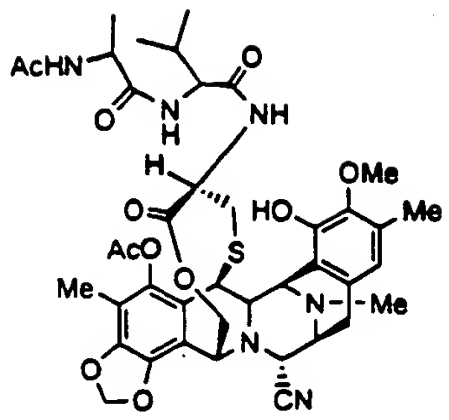
Compound **3n** (from **2n**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.21 (m, 5H), 6.37 (s, 1H), 6.02 (dd, 2H), 5.67 (s, 1H), 5.04 (d, 1H), 4.52 (bp, 1H), 4.24-4.22 (m, 3H), 4.11 (dd, 1H), 3.73 (s, 3H), 3.62 (dd, 2H), 3.42-3.41 (m, 2H), 3.19-3.18 (m, 1H), 3.03-2.83 (m, 2H), 2.34-2.30 (m, 1H), 2.30 (s, 3H), 2.18 (s, 3H), 2.05-2.02 (m, 1H), 2.02 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 168.5, 147.7, 145.6, 142.9, 141.0, 140.4, 140.1, 130.6, 129.3, 128.2, 128.2, 126.8, 120.7, 118.2, 118.0, 113.8, 113.3, 101.9, 99.1, 61.5, 60.1, 59.6, 59.5, 59.2, 54.7, 51.3, 41.6, 41.5, 33.4, 23.8, 20.5, 15.3, 9.6. ESI-MS m/z: Calcd. for $C_{38}H_{40}N_4O_8S$: 712.3. Found ($M+H^+$): 713.3.



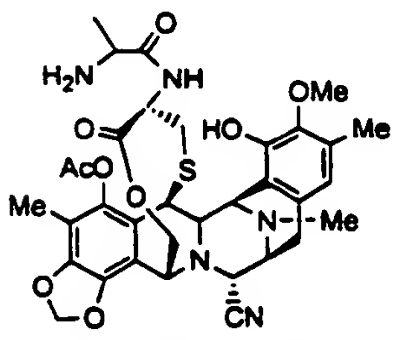
Compound **3p** (from **7**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (bp. 1H), 6.51 (s, 1H), 6.05 (dd, 2H), 5.03 (d, 1H), 4.64 (dt, 1H), 4.55 (bp, 1H), 4.31 (s, 1H), 4.26 (dd, 1H), 4.21 (d, 1H), 4.17 (dd, 1H), 3.76 (s, 3H), 3.49-3.42 (m, 2H), 2.99 (d, 1H), 2.90-2.88 (m, 2H), 2.47-1.97 (m, 3H), 2.32 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H), 0.97 (d, 3H), 0.79 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 170.4, 168.5, 147.6, 145.9, 143.1, 141.1, 140.5, 130.8, 129.0, 120.8, 120.6, 118.8, 118.0, 113.5, 113.3, 102.0, 61.5, 60.6, 60.2, 60.0, 59.6, 58.6, 54.7, 54.6, 51.9, 42.0, 41.5, 33.0, 31.6, 23.9, 20.4, 19.6, 16.8, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{36}H_{43}N_5O_9S$: 721.3. Found ($M+H^+$): 722.2



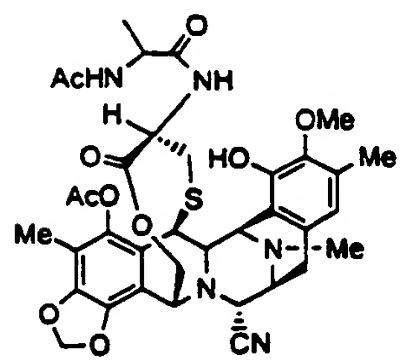
Compound **3s** (from **9** using 9 equiv of TMSCl and NaI. The reaction was quenched with brine and Na_2CO_3): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 1H), 6.55 (s, 1H), 6.05 (dd, 2H), 5.61 (d, 1H), 5.02 (d, 1H), 4.68-4.64 (m, 1H), 4.57 (bp, 1H), 4.29 (s, 1H), 4.27 (dd, 1H), 4.20-4.16 (m, 2H), 4.04 (dd, 1H), 3.79 (s, 3H), 3.52-3.43 (m, 3H), 2.91-2.89 (m, 2H), 2.49 (s, 3H), 2.29-2.02 (m, 3H), 2.29 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.33 (d, 3H), 1.07 (d, 3H), 0.97 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 170.2, 170.2, 168.5, 148.0, 145.9, 143.3, 141.1, 140.4, 130.4, 130.1, 120.4, 120.2, 118.5, 118.0, 113.5, 102.0, 61.5, 60.4, 60.3, 59.4, 58.8, 57.4, 54.7, 54.6, 51.8, 50.9, 42.0, 41.5, 32.7, 32.2, 23.8, 21.8, 20.5, 19.3, 18.0, 16.3, 9.6. ESI-MS m/z: Calcd. for $C_{39}H_{48}N_6O_{10}S$: 792.3. Found ($M+H^+$): 793.3.



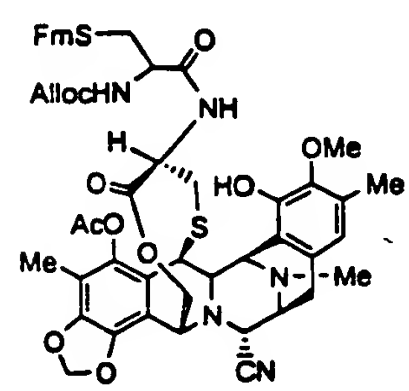
Compound **3t** (from **2t**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.59 (bd, 1H), 6.53 (s, 1H), 6.28-6.22 (m, 1H), 6.04 (dd, 2H), 5.89 (s, 1H), 5.60, 5.58 (2d, 1H), 5.01 (d, 1H), 4.66-4.62 (m, 1H), 4.57 (bp, 1H), 4.50-4.43 (m, 1H), 4.28 (s, 1H), 4.25 (d, 1H), 4.20-4.12 (m, 2H), 4.09-4.04 (m, 1H), 3.78, 3.77 (2s, 3H), 3.47-3.42 (m, 2H), 2.90-2.87 (m, 2H), 2.46 (s, 3H), 2.28-1.98 (m, 3H), 2.28 (s, 3H), 2.16, 2.15 (2s, 3H), 2.03, 2.02 (2s, 3H), 1.98 (s, 3H), 1.36, 1.32 (2d, 3H), 1.05, 1.03 (2d, 3H), 0.93 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 170.1, 169.7, 169.6, 168.5, 148.0, 145.9, 143.2, 141.1, 140.4, 130.6, 129.8, 120.3, 120.2, 118.7, 118.0, 113.4, 102.0, 61.4, 60.3, 60.3, 59.4, 58.8, 57.7, 57.6, 54.6, 54.5, 51.9, 48.9, 48.9, 42.0, 41.5, 32.6, 32.3, 32.2, 23.8, 23.1, 20.5, 19.2, 19.1, 19.1, 18.5, 17.7, 17.7, 16.2, 9.6. ESI-MS m/z: Calcd. for $C_{41}H_{50}N_6O_{11}S$: 834.3. Found ($M+H^+$): 835.3.



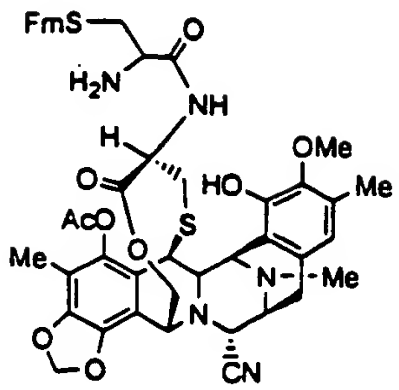
Compound **3v** (from **8**; the reaction was quenched with brine and Na_2CO_3): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (bp, 1H), 6.52 (s, 1H), 6.04 (dd, 2H), 5.03 (d, 1H), 4.58-4.53 (m, 2H), 4.30 (s, 1H), 4.25 (dd, 1H), 4.20-4.14 (m, 2H), 3.76 (s, 3H), 3.45-3.42 (m, 2H), 3.30 (dd, 1H), 2.90-2.88 (m, 2H), 2.38-2.00 (m, 2H), 2.30 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 2.03 (s, 3H), 1.25 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 170.3, 168.4, 147.6, 145.9, 143.1, 141.1, 140.5, 130.8, 129.0, 120.9, 120.5, 118.7, 118.0, 113.5, 113.3, 102.0, 61.5, 60.2, 60.1, 59.6, 58.8, 54.8, 54.6, 52.1, 50.8, 41.9, 41.5, 32.7, 23.9, 21.6, 20.4, 16.1, 9.6. ESI-MS m/z: Calcd. for $C_{34}H_{39}N_5O_9S$: 693.2. Found ($M+H^+$): 694.3.



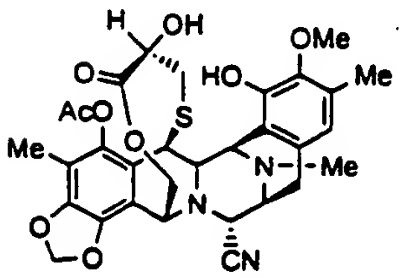
Compound **3w** (from **2w**; the reaction was quenched with brine): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67, 6.55 (2s, 1H), 6.30 (m, 1H), 6.05 (dd, 2H), 5.86, 5.79 (2s, 1H), 5.65, 5.54 (2bd, 1H), 5.03, 5.02 (2d, 1H), 4.60-4.17 (m, 7H), 3.79, 3.76 (2s, 3H), 3.45-3.40 (m, 2H), 2.92-2.85 (bd, 2H), 2.46-1.95 (m, 2H), 2.46, 2.40 (2s, 3H), 2.29, 2.28 (2s, 3H), 2.17, 2.15 (2s, 3H), 2.02 (s, 3H), 1.98, 1.95 (2s, 3H), 1.45, 1.20 (2d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 170.1, 169.9, 169.1, 168.6, 148.2, 147.7, 145.9, 143.2, 141.1, 140.4, 130.9, 130.4, 130.0, 129.8, 120.8, 120.3, 118.8, 118.0, 113.6, 113.4, 102.0, 61.5, 61.4, 60.5, 60.4, 59.3, 59.1, 58.7, 54.8, 54.6, 51.9, 51.7, 48.5, 42.1, 41.9, 41.5, 32.4, 32.3, 23.8, 23.2, 20.5, 19.9, 16.0, 15.8, 9.6. ESI-MS m/z: Calcd. for $C_{36}H_{41}N_5O_{10}S$: 735.3. Found ($M+H^+$): 736.2.



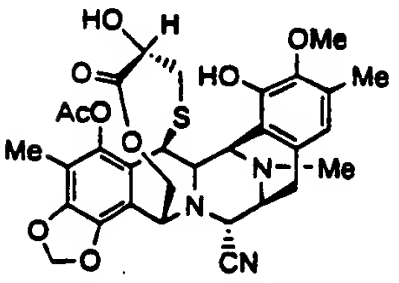
Compound **3y** (from **2y**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.68 (m, 4H), 7.42-7.26 (m, 4H), 6.53 (s, 1H), 6.05 (bd, 1H), 6.04 (dd, 2H), 5.96-5.87 (m, 1H), 5.74 (s, 1H), 5.58 (bd, 1H), 5.38-5.20 (m, 2H), 5.00 (d, 1H), 4.60-4.55 (m, 4H), 4.33-4.08 (m, 6H), 3.73 (s, 3H), 3.44-3.42 (m, 2H), 3.19-3.13 (m, 1H), 3.05-2.83 (m, 5H), 2.38-2.02 (m, 2H), 2.38 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H); ESI-MS m/z: Calcd. for $C_{52}H_{53}N_5O_{11}S_2$: 987.3. Found ($M+H^+$): 988.1.



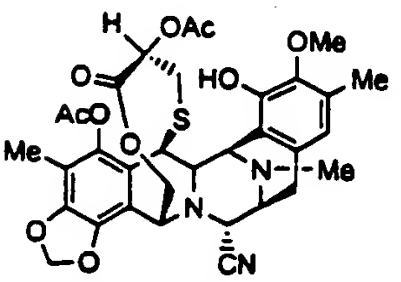
Compound **3z** was also obtained in the reaction of **2y**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, 2H), 7.66 (dd, 2H), 7.42-7.30 (m, 4H), 6.49 (s, 1H), 6.05 (dd, 2H), 5.67 (bp, 1H), 5.02 (d, 1H), 4.59-4.54 (m, 2H), 4.30 (bs, 1H), 4.25-4.23 (dd, 1H), 4.19-4.09 (m, 3H), 3.71 (s, 3H), 3.68-3.43 (m, 2H), 3.33 (dd, 1H), 3.14-2.85 (m, 5H), 2.46 (dd, 1H), 2.35-2.24 (m, 2H), 2.25 (s, 3H), 2.24 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H); ESI-MS m/z: Calcd. for $C_{48}H_{49}N_5O_9S_2$: 903.3. Found ($M+H^+$): 904.2.



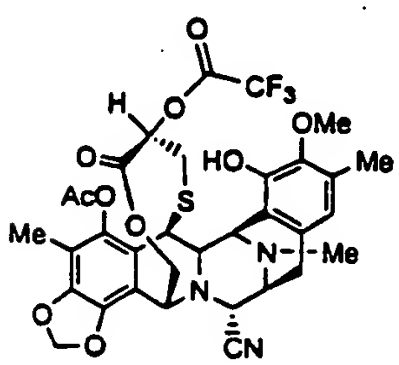
Compound **15** (from **11**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.03 (dd, 2H), 5.74 (s, 1H), 5.04 (d, 2H), 4.54 (bp, 1H), 4.26-4.23 (m, 2H), 4.20-4.14 (m, 2H), 4.02-3.96 (m, 1H), 3.78 (s, 3H), 3.42-3.39 (m, 2H), 2.93-2.90 (m, 2H), 2.31-2.03 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H); ESI-MS m/z: Calcd. for $C_{31}H_{33}N_3O_9S$: 623.2. Found ($M+H^+$): 624.2.



Compound **16*** (from **12***): ^{1}H NMR (300 MHz, 45°C, $CDCl_3$): δ 6.49 (s, 1H), 6.04 (dd, 2H), 5.67 (s, 1H), 4.94 (bd, 1H), 4.47 (s, 1H), 4.24-4.17 (m, 3H), 4.05 (d, 1H), 3.80 (s, 3H), 3.57-3.55 (m, 2H), 3.40-3.37 (m, 1H), 2.98-2.90 (m, 1H), 2.73 (d, 1H), 2.51-2.47 (bm, 1H), 2.33 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 1.66 (dd, 1H); ESI-MS m/z: Calcd. for $C_{31}H_{33}N_3O_9S$: 623.2. Found ($M+H^+$): 624.3.

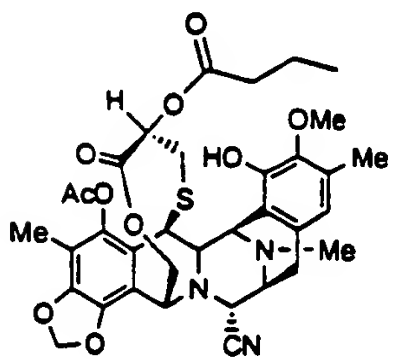


Compound **17a** (from **13a**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 6.04 (dd, 2H), 5.67 (s, 1H), 5.02-4.99 (m, 2H), 4.56 (bp, 1H), 4.27 (s, 1H), 4.25 (dd, 1H), 4.17 (d, 1H), 4.11 (dd, 1H), 3.79 (s, 3H), 3.44-3.41 (m, 2H), 2.88-2.86 (m, 2H), 2.31-1.97 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 168.5, 167.0, 147.2, 145.7, 142.9, 141.1, 140.6, 130.9, 128.7, 121.2, 120.7, 118.1, 118.0, 113.5, 102.0, 71.6, 61.4, 60.2, 60.0, 59.9, 59.0, 54.7, 54.6, 41.6, 41.5, 31.5, 23.9, 20.5, 20.3, 15.8, 9.6. ESI-MS m/z: Calcd. for $C_{33}H_{35}N_3O_{10}S$: 665.2. Found ($M+H^+$): 666.1.

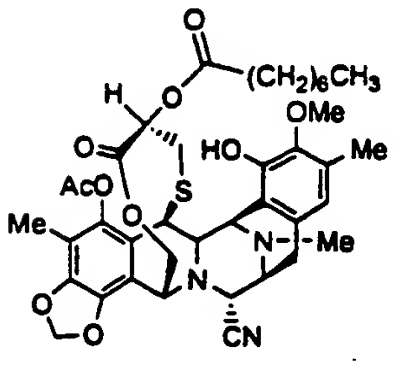


Compound **17b** (from **13b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.46 (s, 1H), 6.05 (dd, 2H), 5.68 (s, 1H), 5.09 (bt, 1H), 5.02 (d, 1H), 4.62 (bp, 1H), 4.31 (s, 1H), 4.24 (dd, 1H), 4.19-4.14 (m, 2H), 3.77 (s, 3H), 3.46-3.40 (m, 2H), 2.93-2.75 (m, 2H), 2.44-2.37 (dd, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 2.16 (s, 3H), 2.10-2.04 (m, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 164.9, 147.0, 145.9, 142.9, 141.2, 140.7, 132.2 (**CF3?**), 130.6, 129.5, 125.1(**CF3?**), 121.6, 120.5(**CF3?**),

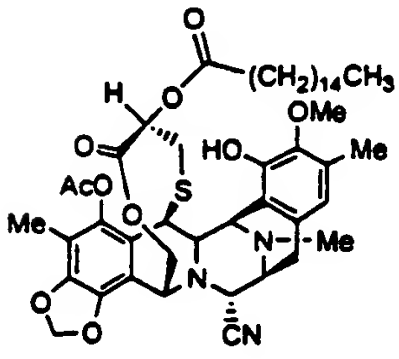
118.0, 117.3, 113.7, 113.3, 113.3(CF3?), 102.1, 74.8, 61.4, 60.6, 60.1, 59.9, 58.9, 54.6, 41.7, 41.6, 31.0, 23.9, 20.4, 15.5, 9.6. ESI-MS m/z: Calcd. for $C_{33}H_{32}F_3N_3O_{10}S$: 719.2. Found ($M+H^+$): 720.2.



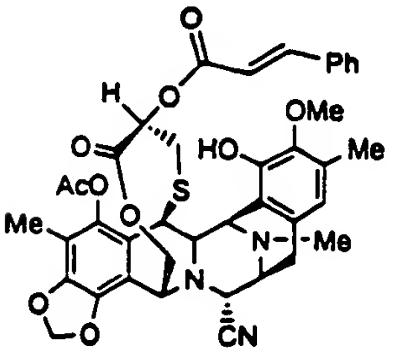
Compound **17c** (from **13c**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.47 (s, 1H), 6.04 (dd, 2H), 5.66 (s, 1H), 5.02-4.99 (m, 2H), 4.57 (bp, 1H), 4.28 (s, 1H), 4.24 (dd, 1H), 4.18 (d, 1H), 4.11 (dd, 1H), 3.79 (s, 3H), 3.45-3.41 (m, 2H), 2.87-2.85 (m, 2H), 2.31-1.99 (m, 4H), 2.31 (s, 3H), 2.29 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H), 1.67-1.55 (m, 2H), 0.97 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 168.5, 167.0, 147.2, 145.8, 142.9, 141.1, 140.6, 131.0, 128.8, 121.2, 120.8, 118.1, 118.1, 113.6, 113.1, 102.0, 71.4, 61.4, 60.2, 59.9, 59.9, 58.8, 54.8, 54.7, 41.6, 35.9, 31.7, 24.0, 20.4, 18.2, 15.8, 13.7, 9.6. ESI-MS m/z: Calcd. for $C_{33}H_{39}N_3O_{10}S$: 693.2. Found ($M+H^+$): 694.2.



Compound **17e** (from **13e**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.47 (s, 1H), 6.03 (dd, 2H), 5.66 (s, 1H), 5.02-4.98 (m, 2H), 4.56 (bp, 1H), 4.27 (s, 1H), 4.24 (dd, 1H), 4.17 (d, 1H), 4.10 (dd, 1H), 3.79 (s, 3H), 3.44-3.42 (m, 2H), 2.87-2.85 (m, 2H), 2.30-1.98 (m, 4H), 2.30 (s, 3H), 2.29 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H), 1.61-1.57 (m, 2H), 1.31-1.23 (m, 8H), 0.89 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 168.5, 167.0, 147.2, 145.8, 142.9, 141.1, 140.6, 130.0, 128.7, 121.2, 120.8, 118.1, 118.1, 113.6, 113.1, 102.0, 71.4, 61.4, 60.2, 59.9, 58.8, 54.8, 54.7, 41.6, 33.8, 31.7, 31.6, 29.1, 28.9, 24.7, 24.0, 22.6, 20.4, 15.8, 14.1, 9.6. ESI-MS m/z: Calcd. for $C_{39}H_{47}N_3O_{10}S$: 749.3. Found ($M+H^+$): 750.9.

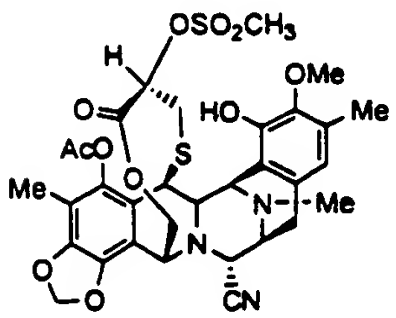


Compound **17f** (from **13f**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 6.04 (dd, 2H), 5.66 (s, 1H), 5.02-4.98 (m, 2H), 4.57 (bp, 1H), 4.28 (s, 1H), 4.25 (dd, 1H), 4.17 (d, 1H), 4.10 (dd, 1H), 3.79 (s, 3H), 3.44-3.40 (m, 2H), 2.87-2.85 (m, 2H), 2.37-1.98 (m, 4H), 2.31 (s, 3H), 2.29 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H), 1.62-1.55 (m, 2H), 1.35-1.26 (m, 24H), 0.88 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 168.6, 167.1, 147.2, 145.7, 142.8, 141.0, 140.6, 130.9, 128.7, 121.2, 120.7, 118.1, 117.9, 113.5, 113.1, 102.0, 71.4, 61.4, 60.3, 59.8, 58.8, 54.7, 54.6, 41.6, 33.8, 31.9, 31.6, 29.7, 29.5, 29.4, 29.3, 29.2, 24.6, 23.9, 22.7, 20.5, 15.9, 14.1, 9.6. ESI-MS m/z: Calcd. for $C_{47}H_{63}N_3O_{10}S$: 861.4. Found ($M+H^+$): 862.3.

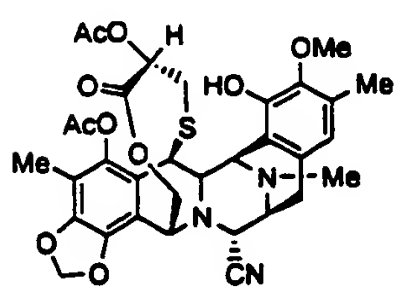


Compound **17h** (from **13h**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, 1H), 7.55-7.52 (m, 2H), 7.43-7.40 (m, 3H), 6.51 (s, 1H), 6.28 (d, 1H), 6.05 (dd, 2H), 5.70 (s, 1H), 5.17 (bt, 1H), 5.04 (d, 1H), 4.58 (bp, 1H), 4.30 (s, 1H), 4.26 (d, 1H), 4.20 (d, 1H), 4.14 (dd, 1H), 3.79 (s, 3H), 3.45 (d, 1H), 3.42-3.39 (m, 1H), 2.92-2.80 (m, 2H), 2.42 (dd, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.15 (s, 3H), 2.09-2.04 (m, 1H), 2.04 (s, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 168.5, 167.0, 165.6, 147.2, 145.8, 145.6, 142.9, 141.1, 140.6, 134.5, 131.1, 130.4, 128.9, 128.8, 128.1, 121.1, 120.8, 118.1, 118.0, 117.4, 113.6, 113.1, 102.0, 71.9, 61.5, 60.3, 59.9, 58.7, 54.7, 54.7, 41.7, 41.6, 31.8, 24.0, 20.4, 15.9, 9.6. ESI-MS m/z: Calcd. for $C_{40}H_{39}N_3O_{10}S$: 753.2. Found ($M+H^+$): 754.7.



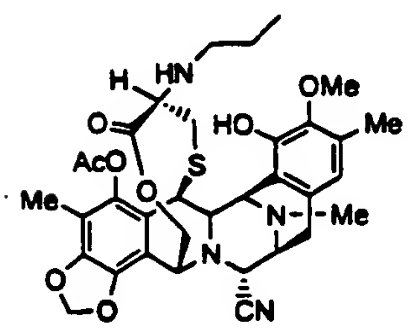
Compound **17ll** (from **13ll**): ^1H NMR (300 MHz, $CDCl_3$): δ 6.43 (s, 1H), 6.04 (dd, 2H), 5.70 (s, 1H), 5.00 (d, 1H), 4.94-4.90 (m, 1H), 4.59 (bp, 1H), 4.28 (s, 1H), 4.24 (d, 1H), 4.17-4.11 (m, 2H), 3.78 (s, 3H), 3.46 (d, 1H), 3.45-3.39 (m, 2H), 3.10 (s, 3H), 2.94-2.78 (m, 2H), 2.50-2.42 (m, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 2.17 (s, 3H), 2.08-2.03 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 166.9, 147.8, 146.1, 143.2, 141.4, 140.8, 130.7, 129.4, 121.3, 120.5, 118.2, 118.0, 113.6, 113.3, 102.3, 77.4, 61.4, 61.0, 60.5, 60.1, 59.6, 55.0, 54.8, 41.8, 41.7, 39.6, 33.0, 24.3, 20.6, 16.0, 9.8. ESI-MS m/z: Calcd. for $C_{32}H_{35}N_3O_{11}S_2$: 701.2. Found ($M+Na^+$): 724.6.



Compound **18a*** (from **14a***): ^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6.04 (dd, 2H), 5.69 (s, 1H), 4.50-4.06 (m, 7H), 3.80 (s, 3H), 3.53 (d, 1H), 3.41-3.38 (m, 1H), 2.96-2.87 (m, 1H), 2.75 (d, 1H), 2.33-1.84 (m, 2H), 2.33 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H), 2.02 (s, 3H), 1.94 (s, 3H); ESI-MS m/z: Calcd. for $C_{33}H_{35}N_3O_{10}S$: 665.2. Found ($M+H^+$): 666.7.

Example 8

Method H: To a solution of 1 equiv. of **5** in CH_3CN (0.05M) under Argon at room temperature, were added the amine and 3 equiv. of AcOH. After 40 min. 1.5 equiv. of $NaBH_3CN$ were added and the solution was stirred for 40 min. After this time the reaction mixture was diluted with CH_2Cl_2, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4. Flash chromatography gives pure compounds.

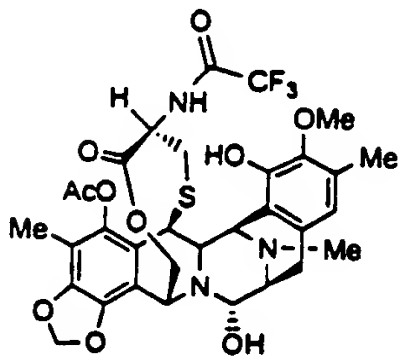


Compound **3o** (using propyl amine): ^1H NMR (300 MHz, $CDCl_3$): δ 6.51 (s, 1H), 6.02 (dd, 2H), 5.71 (s, 1H), 5.01 (d, 1H), 4.53 (bp, 1H), 4.24-4.19 (m, 3H), 4.10 (dd, 1H), 3.77 (s, 3H), 3.41-3.40 (m, 2H), 3.17-3.16 (m, 1H), 3.00-2.82 (m, 2H), 2.46-1.97 (m, 4H), 2.29 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.44-1.25 (m, 2H), 0.84 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 168.6, 147.6, 145.5, 142.9, 140.8, 140.4, 130.6, 129.1, 120.8, 120.7, 118.2, 113.7, 113.2, 101.9, 61.4, 60.1, 60.0, 59.5, 59.0, 54.7, 54.6, 49.2, 41.5, 32.9, 23.8, 23.3, 20.6, 15.7, 11.7, 9.6. ESI-MS m/z: Calcd. for $C_{34}H_{40}N_4O_8S$: 664.3. Found ($M+H^+$): 665.3.

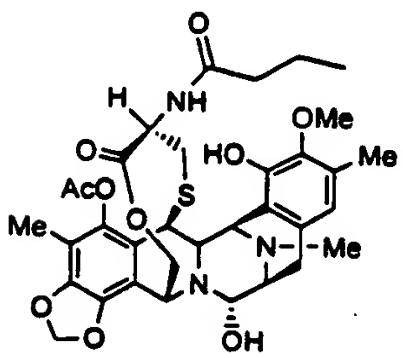
Example 9

Method I: To a solution of 1 equiv. of **3b-i, 3k-l, 3q, 3s, 3u-v, 3x-y** or **15** in CH_3CN/H_2O 3:2 (0.009M) were added 30 equiv. of $AgNO_3$. After 24 h the reaction was

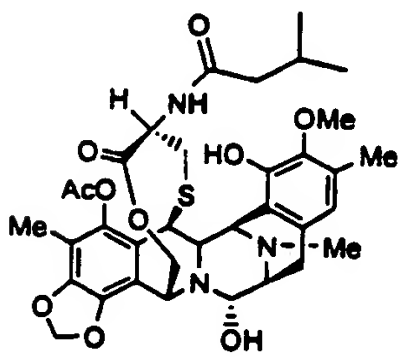
quenched with a mixture 1:1 of saturated solutions of brine and $NaHCO_3$, stirred for 10 min and diluted and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4. Chromatography gives pure compounds **4b-i, 4k-l, 4q, 4s, 4u-v, 4x-y** or **19**.



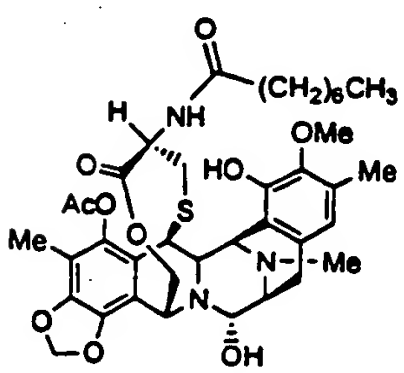
Compound **4b**: t_R= 48.2 min [HPLC, Symmetry 300 C18, 5µm, 250x4.6 mm, λ= 285 nm, flow= 1.2 ml/min, temp= 40°C, grad.: CH_3CNaq.-NH_4OAc (10mM), 1% DEA, pH= 3.0, 10%-60% (90')]; ^1H NMR (300 MHz, $CDCl_3$): δ 6.53 (s, 1H), 6.49 (bd, 1H), 6.02 (dd, 2H), 5.69 (bp, 1H), 5.17 (d, 1H), 4.81 (s, 1H), 4.52-4.46 (m, 3H), 4.16-4.10 (m, 2H), 3.74 (s, 3H), 3.51-3.48 (m, 1H), 3.25-3.20 (m, 1H), 2.83-2.80 (m, 2H), 2.45-2.40 (m, 1H), 2.29-2.02 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 168.6, 156.8, 156.3, 155.7, 147.4, 145.7, 142.9, 141.1, 140.9, 131.2, 129.7, 120.8, 120.7, 117.9, 114.9, 112.7, 101.9, 81.4, 62.0, 60.1, 57.7, 57.6, 56.0, 54.8, 52.9, 42.2, 41.3, 29.7 , 23.6, 20.5, 15.6, 9.6. ESI-MS m/z: Calcd. for $C_{32}H_{34}F_3N_3O_{10}S$: 709.2. Found ($M-H_2O+H^+$): 692.2.



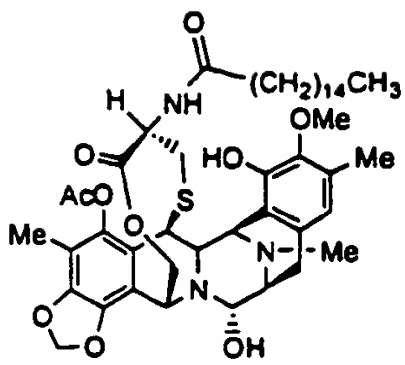
Compound **4c**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.01 (dd, 2H), 5.70 (s, 1H), 5.57 (bd, 1H), 5.15 (d, 1H), 4.77 (s, 1H), 4.61-4.57 (m, 1H), 4.50-4.42 (m, 2H), 4.15-4.07 (m, 2H), 3.77 (s, 3H), 3.49-3.47 (m, 1H), 3.23-3.15 (m, 1H), 2.85-2.82 (m, 2H), 2.32-1.98 (m, 4H), 2.32 (s, 3H), 2.28 (s, 3H), 2.13 (s, 3H), 2.01 (s, 3H), 1.65-1.58 (m, 2H), 0.96 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 170.5, 147.9, 145.6, 143.0, 141.0, 140.8, 131.6, 128.8, 121.0, 120.7, 118.9, 115.3, 101.8, 81.5, 61.6, 60.3, 57.8, 57.6, 56.0, 55.0, 51.9, 42.0, 41.3, 38.3, 32.6, 23.7, 20.5, 18.9, 16.1, 13.8, 9.6. ESI-MS m/z: Calcd. for $C_{34}H_{41}N_3O_{10}S$: 683.2. Found ($M-H_2O+H^+$): 666.3.



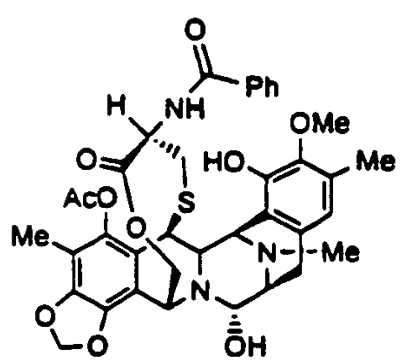
Compound **4d**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.02 (dd, 2H), 5.72 (bs, 1H), 5.55 (bd, 1H), 5.15 (d, 1H), 4.78 (s, 1H), 4.64-4.60 (m, 1H), 4.48-4.42 (m, 2H), 4.17-4.12 (m, 1H), 4.09 (dd, 1H), 3.77 (s, 3H), 3.53-3.48 (m, 1H), 3.27-3.20 (m, 1H), 2.90-2.75 (m, 2H), 2.34-1.91 (m, 5H), 2.34 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H), 2.01 (s, 3H), 0.98 (d, 3H), 0.93 (d, 3H); ESI-MS m/z: Calcd. for $C_{35}H_{43}N_3O_{10}S$: 697.3. Found ($M-H_2O+H^+$): 680.0.



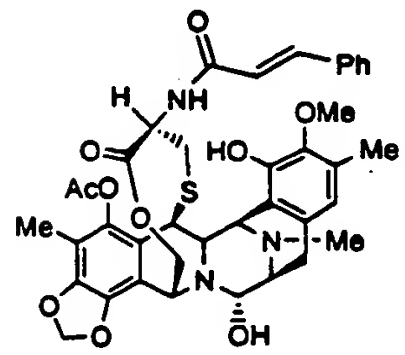
Compound **4e**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.02 (d, 2H), 5.70 (s, 1H), 5.55 (bd, 1H), 5.15 (d, 1H), 4.77 (s, 1H), 4.61-4.55 (m, 1H), 4.50-4.42 (m, 2H), 4.17-4.14 (m, 1H), 4.08 (dd, 1H), 3.77 (s, 3H), 3.51-3.48 (m, 1H), 3.26-3.19 (m, 1H), 2.86-2.79 (m, 2H), 2.32-1.98 (m, 4H), 2.32 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H), 2.01 (s, 3H), 1.65-1.58 (m, 2H), 1.37-1.22 (m, 8H), 0.89 (t, 3H); ESI-MS m/z: Calcd. for $C_{38}H_{49}N_3O_{10}S$: 739.3. Found ($M-H_2O+H^+$): 722.3.



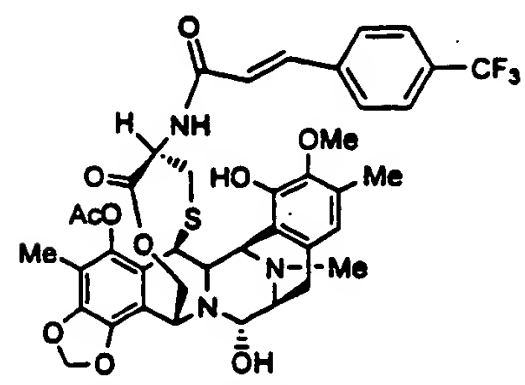
Compound **4f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.02 (dd, 2H), 5.70 (s, 1H), 5.57-5.53 (bd, 1H), 5.14 (d, 1H), 4.77 (s, 1H), 4.58 (ddd, 1H), 4.47-4.43 (m, 2H), 4.18-4.13 (m, 1H), 4.08 (dd, 1H), 3.77 (s, 3H), 3.50-3.46 (m, 1H), 3.25-3.19 (m, 1H), 2.88-2.82 (m, 1H), 2.32-1.95 (m, 4H), 2.32 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H), 2.01 (s, 3H), 1.40-1.20 (m, 26H), 0.88 (t, 3H); ESI-MS m/z: Calcd. for $C_{46}H_{65}N_3O_{10}S$: 851.4. Found ($M-H_2O+H^+$): 834.5.



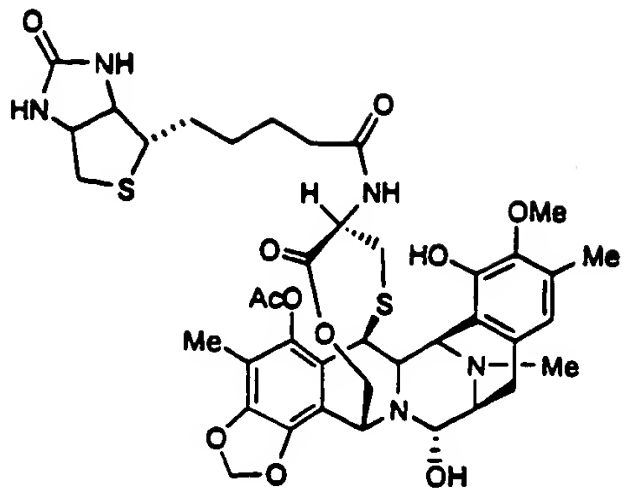
Compound **4g**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.67 (m, 2H), 7.56-7.45 (m, 3H), 6.49 (s, 1H), 6.42 (d, 1H), 6.03 (dd, 2H), 5.66 (s, 1H), 5.20 (d, 1H), 4.82 (s, 1H), 4.73 (dt, 1H), 4.52-4.45 (m, 2H), 4.16-4.10 (m, 2H), 3.61 (s, 3H), 3.52 (bd, 1H), 3.27-3.22 (m, 1H), 2.90-2.85 (m, 2H), 2.62-2.56 (m, 1H), 2.28-1.92 (m, 1H), 2.28 (s, 3H), 2.13 (s, 3H), 2.03 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 168.5, 166.4, 147.6, 145.7, 142.9, 141.1, 140.9, 134.4, 131.5, 129.3, 128.6, 127.0, 125.1, 121.2, 120.5, 115.1, 112.6, 101.8, 81.5, 61.6, 60.1, 57.9, 56.0, 55.0, 53.3, 42.1, 41.3, 32.7, 23.9, 20.4, 15.6, 9.6; ESI-MS m/z: Calcd. for $C_{37}H_{39}N_3O_{10}S$: 717.2. Found ($M-H_2O+H^+$): 699.9.



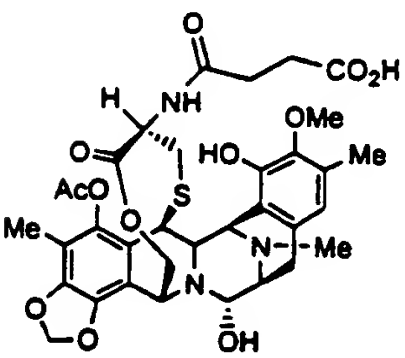
Compound **4h**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, 1H), 7.55-7.51 (m, 2H), 7.44-7.38 (m, 3H), 6.65 (s, 1H), 6.25 (d, 1H), 6.02 (dd, 2H), 5.80 (d, 1H), 5.71 (s, 1H), 5.18 (d, 1H), 4.79 (s, 1H), 4.69 (ddd, 1H), 4.49-4-43 (m, 2H), 4.16-4.09 (m, 2H), 3.68 (s, 3H), 3.51-3.49 (m, 1H), 3.26-3.20 (m, 1H), 2.89-2.86 (m, 2H), 2.52-2.47 (m, 1H), 2.29-2.03 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 168.5, 164.5, 147.9, 145.6, 143.0, 141.8, 141.5, 141.0, 140.8, 134.8, 131.6, 129.7, 129.0, 128.8, 127.9, 121.0, 120.5, 120.1, 118.7, 115.2, 112.7, 101.8, 81.6, 61.7, 60.2, 57.7, 57.6, 56.0, 54.9, 52.7, 42.0, 41.3, 32.5, 23.7, 20.5, 16.3, 9.6. ESI-MS m/z: Calcd. for $C_{39}H_{41}N_3O_{10}S$: 743.2. Found ($M-H_2O+H^+$): 726.3.



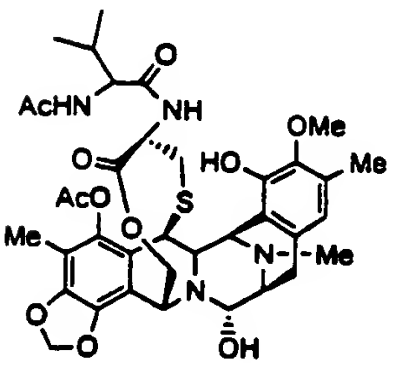
Compound **4i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.65-7.51 (m, 4H), 6.65 (s, 1H), 6.29 (d, 1H), 6.03 (dd, 2H), 5.81 (d, 1H), 5.71 (s, 1H), 5.18 (d, 1H), 4.79 (s, 1H), 4.71-4.67 (m, 1H), 4.49-4.47 (m, 2H), 4.16-4.09 (m, 2H), 3.70 (s, 3H), 3.51-3.49 (m, 1H), 3.23-3.20 (m, 1H), 2.88-2.86 (m, 2H), 2.47-2.33 (m, 1H), 2.30-2.02 (m, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H); ESI-MS m/z: Calcd. for $C_{40}H_{40}N_3F_3O_{10}S$: 811.2. Found ($M-H_2O+H^+$): 794.2.



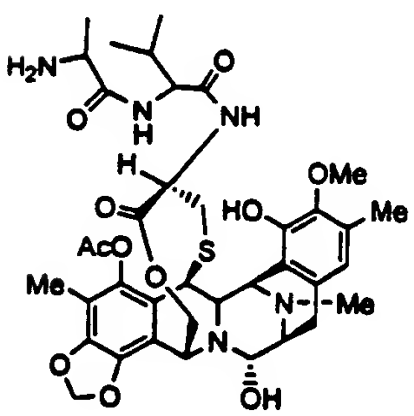
Compound **4k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (bp, 1H), 6.56 (s, 1H), 6.54 (s, 1H), 6.01 (dd, 2H), 5.48 (bd, 1H), 5.14 (d, 1H), 4.75 (s, 1H), 4.68-4.63 (m, 1H), 4.55-4.45 (m, 3H), 4.33 (dd, 1H), 4.22 (bp, 1H), 4.05 (dd, 1H), 3.80 (s, 3H), 3.53-3.45 (m, 1H), 3.22-3.13 (m, 1H), 3.10-3.02 (m, 1H), 2.94-2.84 (m, 3H), 2.66 (d, 1H), 2.34-1.91 (m, 4H), 2.34 (s, 3H), 2.30 (s, 3H), 2.10 (bs, 3H), 2.01 (bs, 3H), 1.75-1.22 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 170.4, 163.7, 148.9, 145.5, 142.7, 141.1, 140.5, 131.8, 128.8, 122.2, 120.3, 112.6, 101.7, 82.0, 62.1, 60.1, 59.7, 57.2, 56.4, 55.7, 55.3, 51.2, 41.9, 41.2, 41.1, 34.3, 32.9, 27.8, 27.5, 24.8, 23.9, 20.7, 16.2, 9.6; ESI-MS m/z: Calcd. for $C_{40}H_{49}N_5O_{11}S_2$: 840.0. Found ($M-H_2O^+$): 822.3.



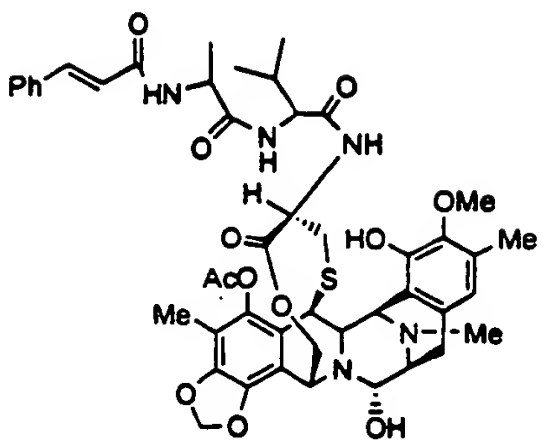
Compound **4l**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.02 (dd, 2H), 5.82-5.72 (bm, 2H), 5.15 (d, 1H), 4.79 (bs, 1H), 4.57-4.45 (m, 3H), 4.22-4.15 (bp, 1H), 4.11 (dd, 1H), 3.78 (s, 3H), 3.59-3.49 (bp, 1H), 3.30-3.23 (bp, 1H), 2.91-2.83 (m, 2H), 2.68-2.45 (m, 4H), 2.35-2.02 (m, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 2.17 (s, 3H), 2.01 (s, 3H); ESI-MS m/z: Calcd. for $C_{34}H_{39}N_3O_{12}S$: 713.2. Found ($M-H_2O+H^+$): 696.2.



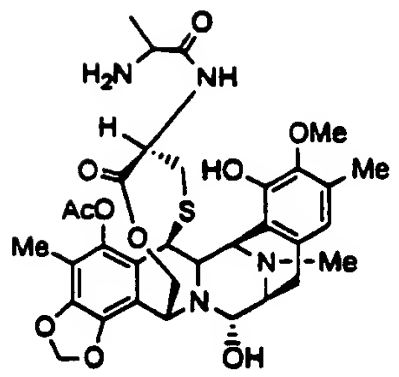
Compound **4q**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55 (s, 1H), 6.07 (d, 1H), 6.02 (d, 2H), 5.75 (s, 1H), 5.64 (d, 1H), 5.15 (d, 1H), 4.78 (s, 1H), 4.67-4.62 (m, 1H), 4.50-4.45 (m, 2H), 4.14-4.09 (m, 3H), 3.80 (s, 3H), 3.51-3.47 (m, 1H), 3.25-3.20 (m, 1H), 2.85-2.82 (m, 2H), 2.50 (s, 3H), 2.29-1.98 (m, 3H), 2.29 (s, 3H), 2.13 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.06 (d, 3H), 0.97 (d, 3H); ESI-MS m/z: Calcd. for $C_{37}H_{46}N_4O_{11}S$: 754.3. Found ($M-H_2O+H^+$): 737.3.



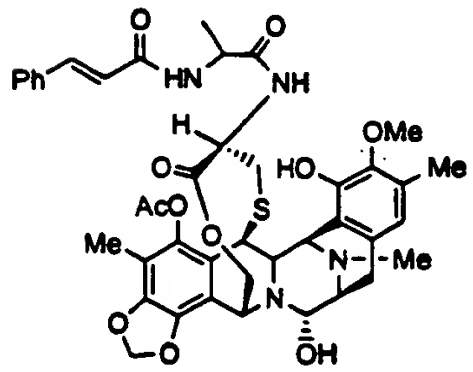
Compound **4s** ESI-MS m/z: Calcd. for $C_{38}H_{49}N_5O_{11}S$: 783.3. Found (M^+): 766.3.



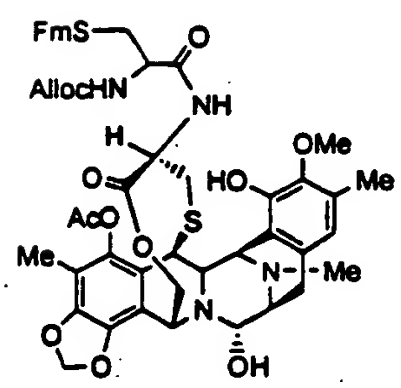
Compound **4u**: ESI-MS m/z: Calcd. for $C_{47}H_{55}N_5O_{12}S$: 914.0. Found ($M-H_2O+H^+$): 897.0.



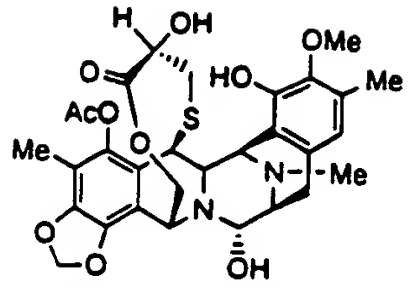
Compound **4v**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.70 (bp, 1H), 6.54 (s, 1H), 6.02 (d, 2H), 5.16 (d, 1H), 4.79 (s, 1H), 4.55-4.48 (m, 3H), 4.15-4.07 (m, 2H), 3.77 (s, 3H), 3.52-3.49 (m, 1H), 3.32-3.21 (m, 2H), 2.85-2.80 (m, 2H), 2.31-2.02 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H), 1.26 (d, 3H); ESI-MS m/z: Calcd. for $C_{33}H_{40}N_4O_{10}S$: 684.2. Found ($M-H_2O+H^+$): 667.2.



Compound **4x**: ESI-MS m/z: Calcd. for $C_{42}H_{46}N_4O_{11}S$: 814.9. Found ($M-H_2O+H^+$): 797.9.



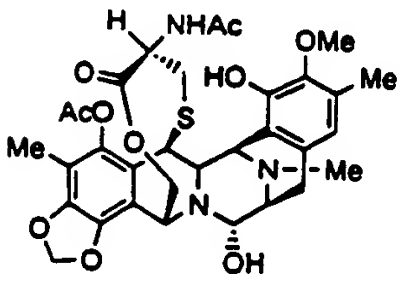
Compound **4y**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.77-7.67 (m, 4H), 7.42-7.28 (m, 4H), 6.55 (s, 1H), 6.18-6.06 (bp, 1H), 6.02 (dd, 2H), 6.03-5.86 (m, 1H), 5.70 (bs, 1H), 5.58 (bd, 1H), 5.35-5.20 (m, 2H), 5.15 (d, 1H), 4.79 (s, 1H), 4.60-4.55 (m, 3H), 4.46 (d, 1H), 4.20-4.11 (m, 4H), 3.73 (s, 3H), 3.49-3.47 (m, 1H), 3.21-3.15 (m, 2H), 3.06-2.70 (m, 6H), 2.38-2.11 (m, 2H), 2.38 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 168.9, 147.8, 145.8, 145.7, 143.0, 141.0, 140.8, 132.5, 131.4, 127.5, 127.1, 127.0, 125.0, 125.0, 120.6, 119.8, 117.9, 115.1, 101.8, 81.4, 65.8, 61.6, 60.3, 57.8, 55.9, 55.0, 54.4, 52.4, 47.0, 42.1, 41.3, 37.2, 36.5, 33.3, 23.6, 20.4, 16.1, 9.6. ESI-MS m/z: Calcd. for $C_{51}H_{54}N_4O_{12}S_2$: 978.3. Found ($M-H_2O+H^+$): 961.3.



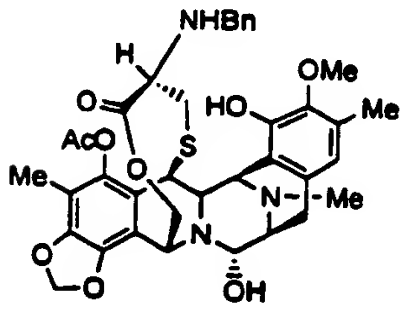
Compound **19**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.58 (s, 1H), 6.01 (dd, 2H), 5.71 (s, 1H), 5.16 (d, 1H), 4.76 (s, 1H), 4.47-4.43 (m, 2H), 4.15-4.11 (m, 1H), 4.08 (dd, 1H), 4.01-3.96 (m, 1H), 3.78 (s, 3H), 3.49-3.45 (m, 1H), 3.21-3.17 (m, 1H), 2.88-2.83 (m, 2H), 2.35-2.02 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 2.17 (s, 3H), 2.02 (s, 3H); ESI-MS m/z: Calcd. for $C_{30}H_{34}N_2O_{10}S$: 614.2. Found ($M-H_2O+H^+$): 597.1.

Example 10

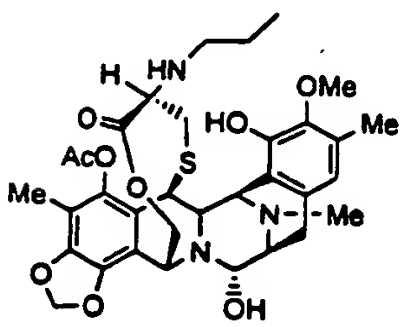
Method J: To a solution of 1 equiv. of **3a, 3n-p, 3r, 3t, 17a, 17cc, 17e-f, 17h, 17ll** or **18a*** in THF/H_2O 4:1 (0.03M) were added 5 equiv. of CuBr. After 24 h the reaction was diluted with CH_2Cl_2, washed with saturated solutions of $NaHCO_3$ and brine, and the organic layer dried with Na_2SO_4. Chromatography gives pure compounds **4a, 4n-p, 4r, 4t, 21a, 21c, 21e-f, 21h, 21ll** or **22a***.



Compound **4a**: t_R= 24.6 min [HPLC, Symmetry 300 C18, 5μm, 250x4.6 mm, λ= 285 nm, flow= 1.2 ml/min, temp= 40°C, grad.: CH_3CNaq.-NH_4OAc (10mM), 1% DEA, pH= 3.0, 10%-60% (90')]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (s, 1H), 6.02 (dd, 2H), 5.79 (bs, 1H), 5.60 (bd, 1H), 5.15 (d, 1H), 4.77 (s, 1H), 4.56 (ddd, 1H), 4.46-4.43 (m, 2H), 4.15 (dd, 1H), 4.09 (dd, 1H), 3.77 (s, 3H), 3.49-3.47 (m, 1H), 3.23-3.20 (m, 1H), 2.91-2.76 (m, 2H), 2.31-2.11 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H), 2.01 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 168.8, 168.5, 148.0, 145.6, 143.0, 141.0, 140.7, 131.5, 128.8, 120.9, 120.6, 118.9, 115.2, 112.7, 101.8, 81.5, 61.6, 60.2, 57.7, 57.4, 55.9, 55.0, 52.1, 52.0, 41.3, 32.4, 23.6, 22.9, 20.5, 16.1, 9.5. ESI-MS m/z: Calcd. for $C_{32}H_{37}N_3O_{10}S$: 655.2. Found ($M-H_2O+H^+$): 638.1.

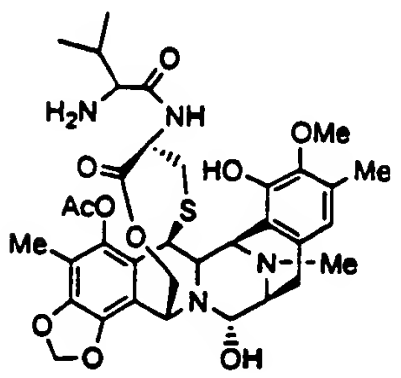


Compound **4n**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.21 (m, 5H), 6.39 (s, 1H), 5.99 (dd, 2H), 5.66 (s, 1H), 5.16 (d, 1H), 4.74 (s, 1H), 4.52 (d, 1H), 4.44 (bp, 1H), 4.12 (d, 1H), 4.03 (dd, 1H), 3.73 (s, 3H), 3.64 (dd, 2H), 3.48-3.47 (m, 1H), 3.21-3.17 (m, 2H), 2.95 (d, 1H), 2.84-2.75 (m, 1H), 2.35-2.30 (m, 1H), 2.30 (s, 3H), 2.16 (s, 3H), 2.07-2.01 (m, 1H), 2.01 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 168.6, 147.6, 145.4, 142.8, 140.9, 140.8, 140.2, 131.3, 130.8, 129.1, 128.8, 128.2, 126.8, 121.4, 120.9, 117.9, 115.6, 112.4, 101.7, 81.8, 60.9, 60.1, 59.5, 57.8, 57.6, 56.1, 54.9, 51.4, 41.8, 41.3, 33.3, 23.6, 20.6, 15.2, 9.6. ESI-MS m/z: Calcd. for $C_{37}H_{41}N_3O_9S$: 703.3. Found ($M-H_2O+H^+$): 686.7.

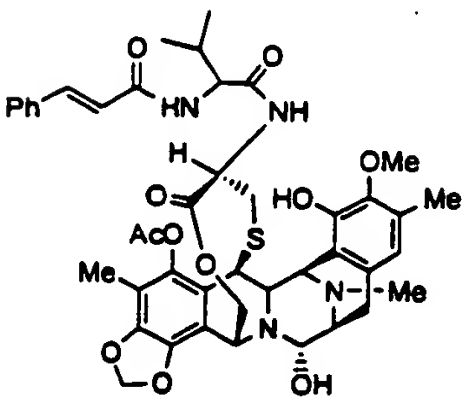


Compound **4o**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.53 (s, 1H), 6.00 (dd, 2H), 5.69 (bp, 1H), 5.14 (d, 1H), 4.74 (s, 1H), 4.44-4.49 (m, 2H), 4.13 (bd, 1H), 4.04 (dd, 1H), 3.78 (s, 3H), 3.49-3.47 (m, 1H), 3.22-3.16 (m, 2H), 2.96-2.75 (m, 2H), 2.51-2.02 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H), 2.02 (s,

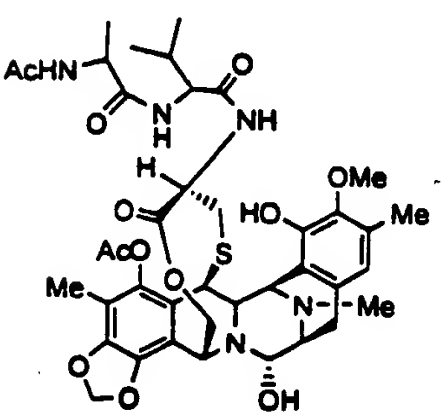
3H), 1.42-1.25 (m, 2H), 0.86 (t, 3H); ESI-MS m/z: Calcd. for $C_{33}H_{41}N_3O_9S$: 655.3. Found ($M-H_2O+H^+$): 638.3.



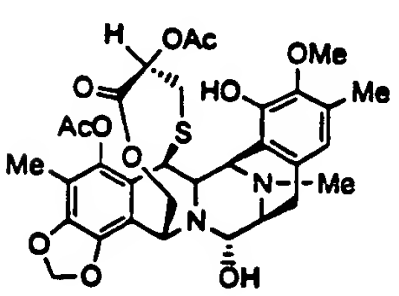
Compound **4p**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (bp. 1H), 6.52 (s, 1H), 6.02 (dd, 2H), 5.67 (bp, 1H), 5.16 (d, 1H), 4.80 (s, 1H), 4.63-4.60 (m, 1H), 4.49 (d, 1H), 4.45 (bp, 1H), 4.16 (d, 1H), 4.08 (dd, 1H), 3.77 (s, 3H), 3.52-3.9 (m, 1H), 3.25-3.20 (m, 1H), 3.00 (d, 1H), 2.85-2.82 (m, 2H), 2.32-2.02 (m, 3H), 2.32 (s, 3H), 2.29 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H), 0.99 (d, 3H), 0.81 (d, 3H); ESI-MS m/z: Calcd. for $C_{35}H_{44}N_4O_{10}S$: 712.3. Found ($M-H_2O+H^+$): 695.2



Compound **4r**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, 1H), 7.49-7.46 (m, 2H), 7.36-7.34 (m, 3H), 6.58 (s, 1H), 6.42 (d, 1H), 6.34 (d, 1H), 6.01 (dd, 2H), 5.79 (s, 1H), 5.69 (d, 1H), 5.15 (d, 1H), 4.78 (s, 1H), 4.70-4.65 (m, 1H), 4.50-4.47 (m, 2H), 4.28 (dd, 1H), 4.15 (d, 1H), 4.10 (dd, 1H), 3.81 (s, 3H), 3.49 (d, 1H), 3.25-3.22 (m, 1H), 2.85-2.83 (m, 2H), 2.57 (s, 3H), 2.28-2.14 (m, 3H), 2.28 (s, 3H), 2.14 (s, 3H), 2.01 (s, 3H), 1.10 (d, 3H), 1.01 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 170.0, 168.6, 165.2, 148.0, 145.7, 143.2, 141.12, 140.84, 134.8, 131.2, 129.9, 129.6, 128.8, 127.8, 120.8, 120.7, 120.6, 118.4, 115.3, 112.7, 101.8, 81.5, 61.7, 60.4, 57.8, 57.7, 57.5, 56.0, 55.0, 52.0, 42.2, 41.3, 32.7, 32.6, 23.7, 20.5, 19.2, 18.0, 16.4, 9.6. ESI-MS m/z: Calcd. for $C_{44}H_{50}N_4O_{11}S$: 842.9. Found ($M-H_2O+H^+$): 825.3.

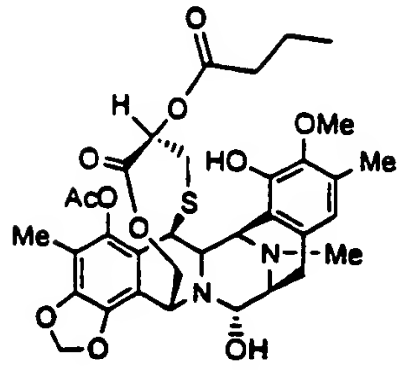


Compound **4t**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.54 (s, 1H), 6.49 (d, 1H), 6.21-6.16 (m, 1H), 6.07-5.96 (m, 2H), 5.78 (s, 1H), 5.63 (bd, 1H), 5.14 (d, 1H), 4.81, 4.78 (2s, 1H), 4.64-4.60 (m, 1H), 4.53-4.08 (m, 6H), 3.78, 3.7s (2s, 3H), 3.65-3.45 (m, 1H), 3.33-3.22 (m, 1H), 2.90-2.66 (m, 2H), 2.48 (s, 3H), 2.28-1.99 (m, 3H), 2.28 (s, 3H), 2.16, 2.13 (2s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.37, 1.34 (2d, 3H), 1.08-1.03 (m, 3H), 0.96-0.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 170.1, 169.6, 169.5, 169.5, 168.7, 147.9, 145.7, 143.1, 141.0, 140.8, 131.3, 129.6, 120.7, 120.4, 118.5, 115.2, 112.6, 101.8, 81.4, 61.6, 60.4, 60.3, 57.7, 57.6, 57.5, 55.9, 54.9, 51.9, 48.9, 48.9, 42.2, 41.3, 32.5, 32.3, 23.6, 23.2, 20.5, 19.2, 19.1, 18.6, 17.7, 17.6, 16.3, 9.6ESI-MS m/z: Calcd. for $C_{40}H_{51}N_5O_{12}S$: 825.3. Found ($M-H_2O+H^+$): 808.3.

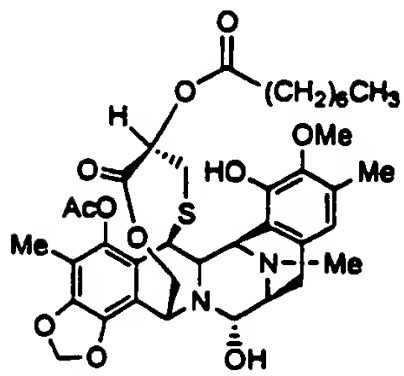


Compound **21a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.52 (s, 1H), 6.01 (dd, 2H), 5.64 (s, 1H), 5.13 (d, 1H), 5.00 (t, 1H), 4.76 (s, 1H), 4.48-4.45 (m, 2H), 4.15-4.12 (m, 1H), 4.02 (dd, 1H), 3.79 (s, 3H), 3.50-3.47 (m, 1H), 3.22-3.17 (m, 1H), 2.82-2.79 (m, 2H), 2.30-1.98 (m, 2H), 2.30 (s, 3H), 2.29 (s, 3H), 2.15 (s,

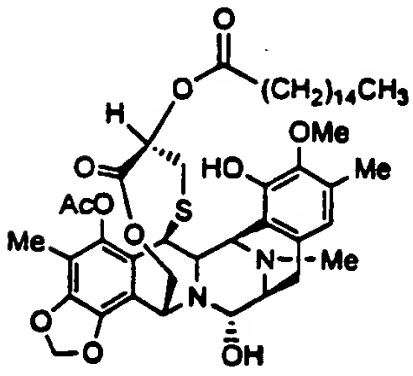
3H), 2.02 (s, 3H), 1.98 (s, 3H); ESI-MS m/z: Calcd. for $C_{32}H_{36}N_2O_{11}S$: 656.2. Found ($M-H_2O+H^+$): 639.2.



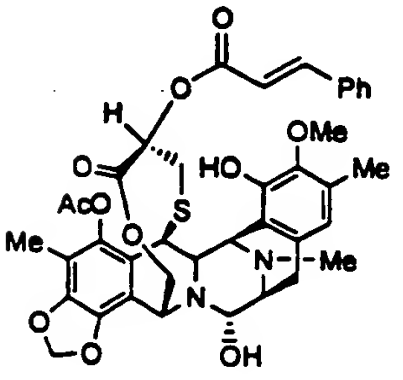
Compound **21c**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.45 (s, 1H), 6.01 (dd, 2H), 5.63 (s, 1H), 5.13 (d, 1H), 5.03 (t, 1H), 4.77 (s, 1H), 4.50-4.48 (m, 2H), 4.14 (bd, 1H), 4.02 (dd, 1H), 3.79 (s, 3H), 3.51-3.49 (bd, 1H), 3.21-3.12 (m, 1H), 2.85-2.75 (m, 2H), 2.31-2.02 (m, 4H), 2.31 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H), 2.02 (s, 3H), 1.66-1.56 (m, 2H), 0.97 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 168.6, 166.9, 147.1, 145.6, 142.8, 141.1, 131.8, 128.6, 125.1, 121.4, 115.4, 101.8, 81.5, 71.6, 61.2, 60.2, 58.2, 57.9, 56.1, 55.0, 41.8, 41.4, 36.0, 31.6, 23.9, 20.4, 18.3, 15.8, 13.7, 9.6. ESI-MS m/z: Calcd. for $C_{34}H_{40}N_2O_{11}S$: 684.2. Found ($M-H_2O+H^+$): 667.2.



Compound **21e**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6.01 (dd, 2H), 5.63 (s, 1H), 5.13 (d, 1H), 5.02 (t, 1H), 4.76 (s, 1H), 4.47-4.46 (m, 2H), 4.13 (dd, 1H), 4.02 (dd, 1H), 3.79 (s, 3H), 3.50-3.49 (m, 1H), 3.21-3.19 (m, 1H), 2.81-2.78 (m, 2H), 2.30-2.02 (m, 4H), 2.30 (s, 3H), 2.29 (s, 3H), 2.13 (s, 3H), 2.02 (s, 3H), 1.62-1.54 (m, 2H), 1.32-1.25 (m, 8H), 0.90 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 168.6, 166.9, 147.1, 145.5, 142.8, 141.1, 141.0, 131.7, 128.6, 121.4, 117.9, 115.4, 112.3, 101.8, 81.5, 71.5, 61.2, 60.2, 58.1, 57.9, 56.1, 55.0, 41.8, 41.4, 33.9, 31.7, 31.6, 29.1, 28.9, 24.7, 23.9, 22.6, 20.4, 15.8, 14.1, 9.6. ESI-MS m/z: Calcd. for $C_{38}H_{48}N_2O_{11}S$: 740.3. Found ($M-H_2O+H^+$): 723.2.

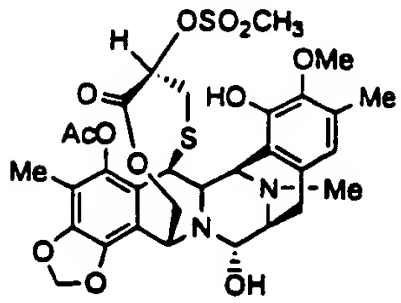


Compound **21f**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 6.01 (dd, 2H), 5.63 (s, 1H), 5.13 (d, 1H), 5.02 (t, 1H), 4.77 (bs, 1H), 4.50-4.48 (m, 2H), 4.16-4.12 (m, 1H), 4.02 (dd, 1H), 3.79 (s, 3H), 3.51-3.49 (m, 1H), 3.22-3.19 (m, 1H), 2.82-2.77 (m, 2H), 2.37-2.02 (m, 7H), 2.30 (s, 3H), 2.29 (s, 3H), 2.02 (s, 3H), 1.65-1.59 (m, 2H), 1.40-1.16 (m, 24H), 0.88 (t, 3H); ESI-MS m/z: Calcd. for $C_{46}H_{64}N_2O_{10}S$: 852.4. Found ($M-H_2O+H^+$): 835.4.

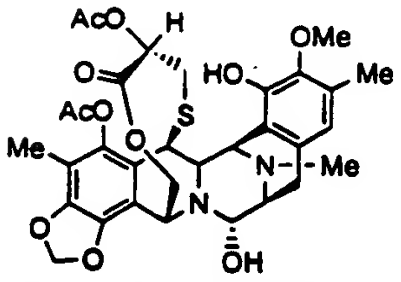


Compound **21h**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, 1H), 7.55-7.52 (m, 2H), 7.42-7.40 (m, 3H), 6.54 (s, 1H), 6.30 (d, 1H), 6.02 (dd, 2H), 5.65 (s, 1H), 5.19-5.16 (m, 2H), 4.79 (s, 1H), 4.50-4.49 (m, 2H), 4.15 (d, 1H), 4.05 (dd, 1H), 3.79 (s, 3H), 3.51 (d, 1H), 3.22-3.19 (m, 1H), 2.89-2.76 (m, 2H), 2.45-2.41 (m, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.13 (s, 3H), 2.13-2.03 (m, 1H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 166.9, 165.7, 147.1, 145.5, 145.4, 142.8, 141.1,

141.0, 134.6, 131.9, 130.3, 128.9, 128.1, 121.3, 117.6, 115.4, 112.3, 101.8, 81.5, 72.0, 61.2, 60.3, 58.2, 57.9, 56.1, 55.0, 41.9, 41.4, 31.8, 23.9, 20.4, 15.9, 9.6. ESI-MS m/z: Calcd. for $C_{39}H_{40}N_2O_{11}S$: 744.2. Found ($M-H_2O+H^+$): 727.2.



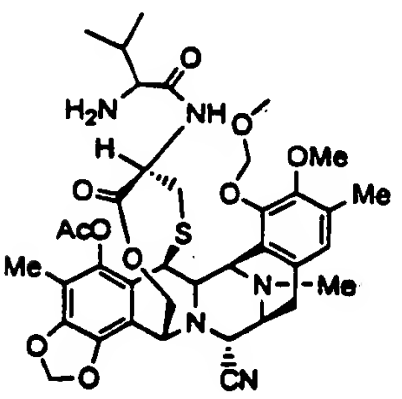
Compound **21ll**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (s, 1H), 6.01 (dd, 2H), 5.68 (s, 1H), 5.12 (d, 1H), 4.92 (t, 1H), 4.78 (s, 1H), 4.53-4.42 (m, 2H), 4.15-4.03 (m, 2H), 3.78 (s, 3H), 3.51-3.48 (m, 1H), 3.24-3.20 (m, 1H), 3.10 (s, 3H), 2.83-2.78 (m, 2H), 2.50-2.42 (m, 1H), 2.31 (s, 3H), 2.30 (s, 3H), 2.17 (s, 3H), 2.08-2.03 (m, 1H), 2.03 (s, 3H); ESI-MS m/z: Calcd. for $C_{31}H_{36}N_2O_{12}S_2$: 692.2. Found ($M-H_2O+H^+$): 675.2.



Compound **22a***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 6.02 (dd, 2H), 5.67 (s, 1H), 4.73 (bp, 1H), 4.71 (s, 1H), 4.48-4.38 (m, 4H), 4.12-4.10 (m, 1H), 3.80 (s, 3H), 3.61-3.59 (m, 1H), 3.22-3.18 (m, 1H), 2.89-2.80 (m, 1H), 2.70 (d, 1H), 2.33-1.86 (m, 2H), 2.33 (s, 3H), 2.30 (s, 3H), 2.12 (s, 3H), 2.01 (s, 3H), 1.94 (s, 3H); ESI-MS m/z: Calcd. for $C_{32}H_{36}N_2O_{11}S$: 656.2. Found ($M-H_2O+H^+$): 639.2.

Example 11

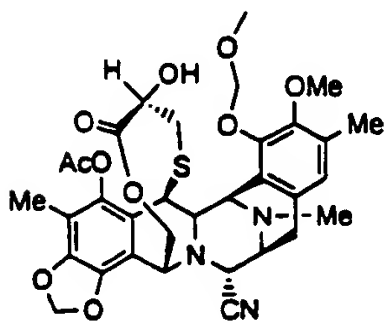
Method K: A solution of **7** in CH_2Cl_2/H_2O/TFA 2:1:4 (0.013M) was stirred for 15 min at RT. Then the reaction was diluted with CH_2Cl_2, neutralized with a saturated solution of $NaHCO_3$ and Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4. Flash chromatography (CH_2Cl_2/MeOH) gives pure **2p**.



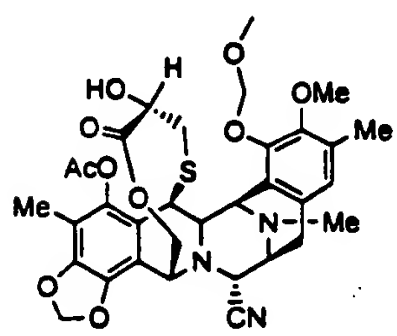
Compound **2p**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (bp. 1H), 6.72 (s, 1H), 6.05 (dd, 2H), 5.15 (dd, 2H), 5.03 (d, 1H), 4.66-4.63 (m, 1H), 4.54 (bp, 1H), 4.35 (d, 1H), 4.32 (s, 1H), 4.23 (d, 1H), 4.17 (dd, 1H), 3.75 (s, 3H), 3.56 (s, 3H), 3.49-3.42 (m, 2H), 3.04 (d, 1H), 2.93-2.90 (m, 2H), 2.28-2.03 (m, 3H), 2.28 (s, 6H), 2.14 (s, 3H), 2.03 (s, 3H), 0.97 (d, 3H), 0.77 (d, 3H); ESI-MS m/z: Calcd. for $C_{38}H_{47}N_5O_{10}S$: 765.3. Found ($M+H^+$): 766.3.

Example 12

Method L: To a solution of **10** in CH_3CN (0.03M) were added 2 equiv. of $NaCNBH_3$ and 4 equiv. of AcOH. After 4 h the reaction was diluted with CH_2Cl_2, neutraliced with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4. Flash chromatography (Hex/EtOAc 2:1)gives pure compounds.



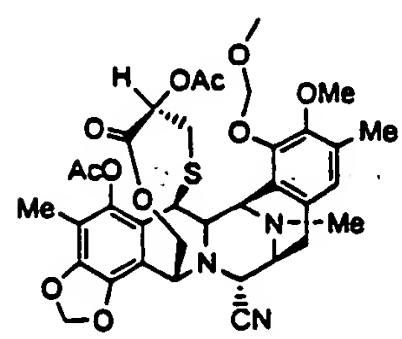
Compound **11**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.77 (s, 1H), 6.03 (dd, 2H), 5.17 (dd, 2H), 5.04 (d, 1H), 4.53 (bp, 1H), 4.34 (d, 1H), 4.27 (s, 1H), 4.20 (d, 1H), 4.19 (dd, 1H), 4.01 (bdd, 1H), 3.77 (s, 3H), 3.57 (s, 3H), 3.55-3.39 (m, 2H), 2.94-2.91 (m, 2H), 2.30-1.98 (m, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 168.6, 149.6, 148.3, 145.7, 141.0, 140.4, 131.6, 130.3, 124.8, 124.7, 120.5, 118.0, 113.3, 102.0, 99.1, 69.8, 61.4, 60.4, 59.6, 59.1, 59.0, 57.4, 54.9, 54.6, 41.4, 41.4, 35.0, 23.8, 20.3, 15.7, 9.6. ESI-MS m/z: Calcd. for $C_{33}H_{37}N_3O_{10}S$: 667.3. Found ($M+H^+$): 668.2.



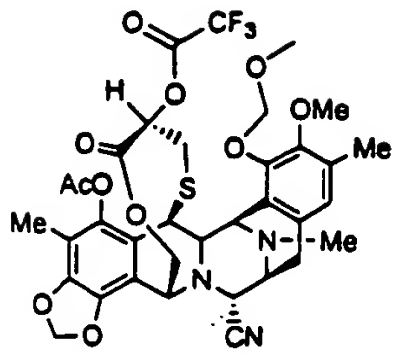
Compound **12***: ^1H NMR (300 MHz, 45°C, $CDCl_3$): δ 6.70 (s, 1H), 6.04 (dd, 2H), 5.17 (dd, 2H), 4.88 (bd, 1H), 4.49 (bs, 1H), 4.33 (bd, 1H), 4.27-4.24 (m, 1H), 4.24 (s, 1H), 4.08 (d, 1H), 3.79 (s, 3H), 3.60-3.55 (m, 2H), 3.56 (s, 3H), 3.42-3.39 (m, 1H), 3.00-2.91 (m, 1H), 2.76 (d, 1H), 2.50-2.42 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.66 (dd, 1H); ESI-MS m/z: Calcd. for $C_{33}H_{37}N_3O_{10}S$: 667.3. Found ($M+H^+$): 668.2.

Example 13

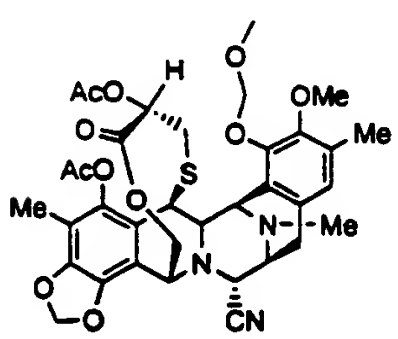
Method M: To a solution of 1 equiv. of **11** for **13a-b** or **12*** for **14a*** in CH_2Cl_2 (0.1M) under Argon were added 30 equiv of pyr. Then the reaction was cold to 0°C and 20 equiv. of the anhydride and 5 equiv. of DMAP were added. After 5 min the reaction was warmed to room temperature and stirred for 24 h. After this time it was quenched with NaCl, extracted with CH_2Cl_2 and the organic layers dried with Na_2SO_4. Flash chromatography gives pure compounds.



Compound **13a** (using Ac_2O): ^1H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.04 (dd, 2H), 5.17 (dd, 2H), 5.02-4.99 (m, 2H), 4.56 (bp, 1H), 4.34 (dd, 1H), 4.27 (s, 1H), 4.18 (d, 1H), 4.14 (dd, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 3.46-3.39 (m, 2H), 2.90-2.87 (m, 2H), 2.30-1.96 (m, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 167.1, 148.9, 148.2, 145.9, 141.2, 140.6, 130.7, 130.7, 125.3, 124.6, 120.8, 118.1, 113.5, 113.1, 102.0, 99.2, 71.6, 61.4, 60.0, 59.9, 59.2, 58.7, 57.4, 55.0, 54.6, 41.5, 31.6, 23.9, 20.3, 20.2, 15.8, 9.6. ESI-MS m/z: Calcd. for $C_{35}H_{39}N_3O_{11}S$: 709.6. Found ($M+H^+$): 710.2.

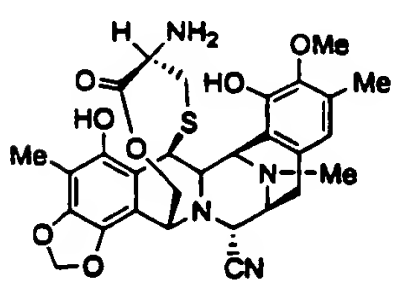


Compound **13b** (using $(F_3CCO)_2O$): ^1H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.04 (dd, 2H), 5.17 (dd, 2H), 5.10 (bt, 1H), 5.02 (d, 1H), 4.62 (bp, 1H), 4.34-4.32 (m, 2H), 4.19-4.15 (m, 2H), 3.76 (s, 3H), 3.56 (s, 3H), 3.47 (d, 1H), 3.44-3.41 (m, 1H), 2.94-2.77 (m, 2H), 2.47-2.37 (m, 1H), 2.31 (s, 3H), 2.23 (s, 3H), 2.17 (s, 3H), 2.07-2.04 (m, 1H), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 164.9, 148.7, 148.2, 145.9, 141.2, 140.7, 131.6, 130.3, 125.7, 124.0, 120.6, 118.0, 113.3, 102.1, 99.2, 74.7, 61.4, 60.5, 60.0, 59.1, 59.2, 58.7, 57.4, 54.9, 54.6, 41.7, 41.5, 31.1, 23.9, 20.2, 15.5, 9.6. ESI-MS m/z: Calcd. for $C_{35}H_{36}F_3N_3O_{11}S$: 763.2. Found ($M+H^+$): 764.2.

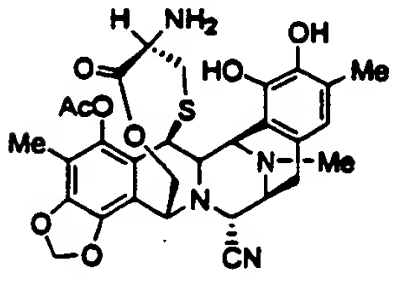


Compound **14a*** (using Ac_2O): ^1H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.05 (dd, 2H), 5.16 (dd, 2H), 4.65-4.10 (m, 7H), 3.79 (s, 3H), 3.57-3.54 (m, 1H), 3.56 (s, 3H), 3.43-3.40 (m, 1H), 2.97-2.88 (m, 1H), 2.78 (d, 1H), 2.33-1.82 (m, 2H), 2.32 (s, 3H), 2.27 (s, 3H), 2.15 (s, 3H), 2.03 (s, 3H), 1.94 (s, 3H); ESI-MS m/z: Calcd. for $C_{35}H_{39}N_3O_{11}S$: 709.6. Found ($M+H^+$): 710.7.

COMPOUNDS **23** AND **24**:



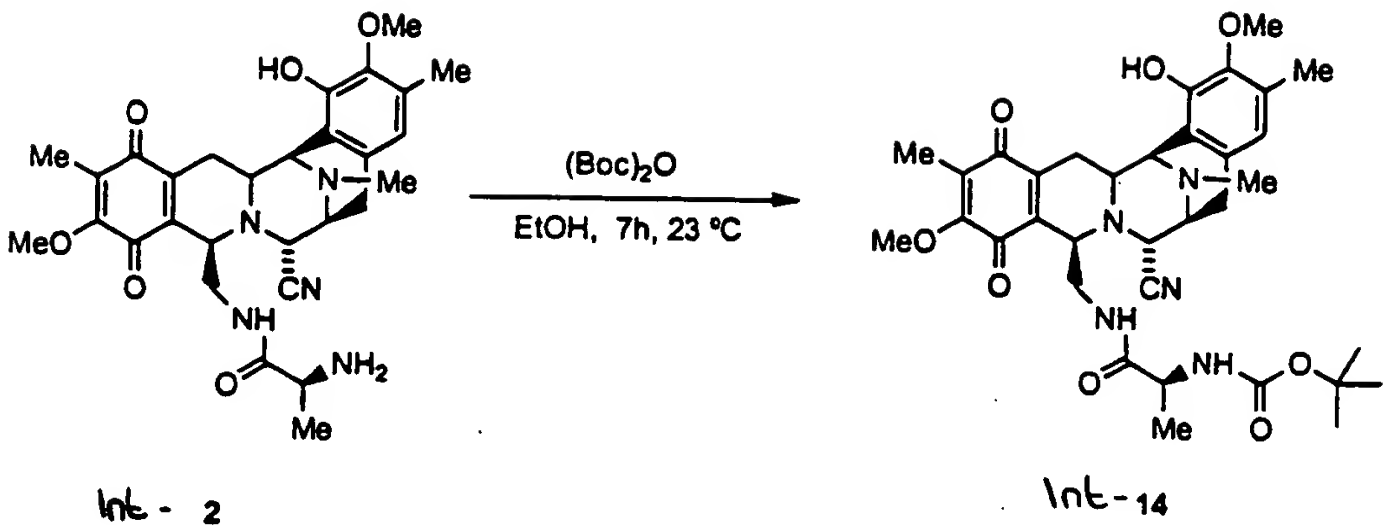
Compound **23**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.52 (s, 1H), 5.95 (dd, 2H), 4.97 (d, 1H), 4.42 (d, 1H), 4.28 (bs, 2H), 4.15 (d, 1H), 4.05 (dd, 1H), 3.78 (s, 3H), 3.51-3.50 (m, 1H), 3.40-3.39 (m, 1H), 3.27 (t, 1H), 2.91-2.89 (m, 2H), 2.38-2.36 (m, 2H), 2.28 (s, 3H), 2.17 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 148.1, 146.2, 146.1, 142.8, 136.2, 130.4, 129.5, 120.8, 118.2, 112.7, 112.7, 107.7, 101.3, 61.1, 60.9, 60.4, 59.4, 58.8, 54.6, 54.6, 53.5, 43.3, 41.4, 33.0, 23.9, 15.7, 8.7; ESI-MS m/z: Calcd. for $C_{29}H_{32}N_4O_7S$: 580.2. Found ($M+H^+$): 581.3.



Compound **24**: ^1H NMR (300 MHz, $CDCl_3$): δ 6.40 (s, 1H), 6.02 (d, 2H), 5.00 (d, 1H), 4.46 (bp, 1H), 4.24 (s, 1H), 4.21-4.14 (m, 3H), 3.39-3.37 (m, 2H), 3.29 (t, 1H), 2.93-2.78 (m, 2H), 2.31-2.03 (m, 2H), 2.31 (s, 3H), 2.25 (bs, 3H), 2.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 168.9, 145.6, 145.3, 140.9, 140.2, 139.3, 126.1, 123.9, 120.2, 119.7, 118.1, 117.7, 113.6, 113.3, 101.9, 61.3, 60.3, 59.1, 59.1, 54.7, 54.6, 53.3, 41.9, 41.4, 33.0, 23.5, 20.5, 16.8, 9.6; ESI-MS m/z: Calcd. for $C_{30}H_{32}N_4O_8S$: 608.2. Found ($M+H^+$): 609.3.

Example 14

Compound **Int-14**



Int - 2

Int-14

To a solution of **Int-2** (21.53 g, 39.17 ml) in ethanol (200 ml), *tert*-butoxycarbonyl anhydride (7.7 g, 35.25 ml) was added and the mixture was stirred for 7 h at 23 °C. Then, the reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 6:4) to give **Int-14** (20.6 g, 81 %) as a yellow solid.

Rf: 0.52 (ethyl acetate:$CHCl_3$ 5:2).

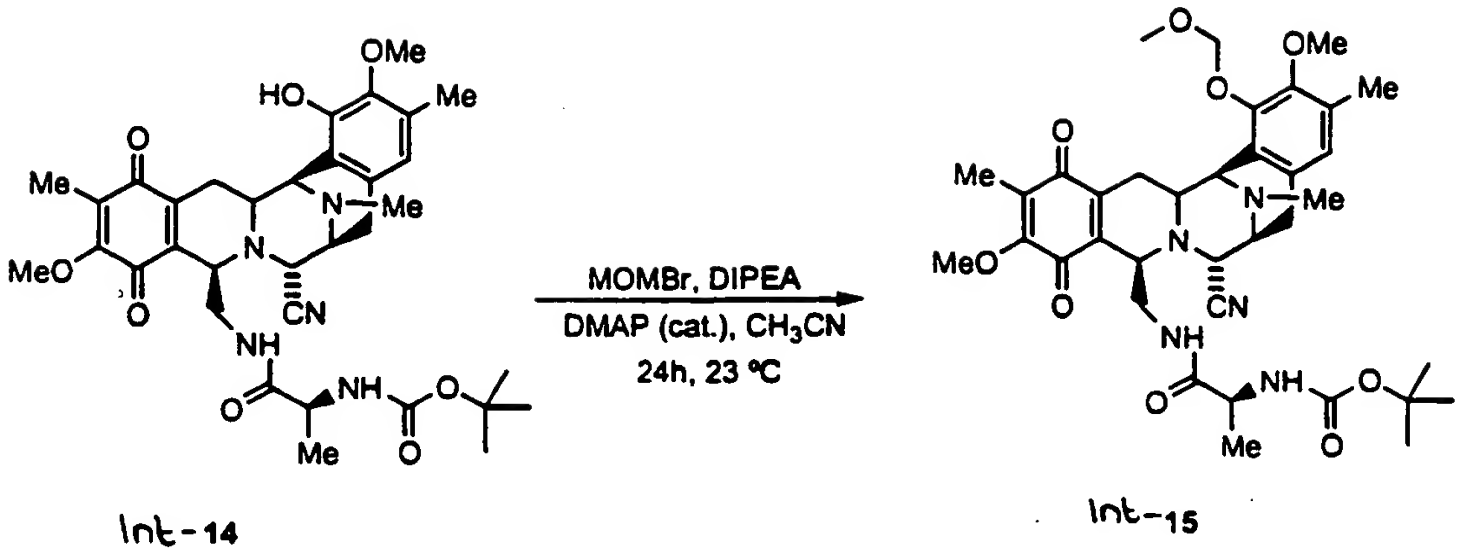
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6. 32 (bs, 1H), 5.26 (bs, 1H), 4.60 (bs, 1H), 4.14 (d, *J*= 2.4 Hz, 1H), 4.05 (d, *J*= 2.4 Hz, 1H), 3.94 (s, 3H), 3.81 (d, *J*= 4.8 Hz, 1H), 3.7 (s, 3H), 3.34 (br d, *J*= 7.2 Hz, 1H), 3.18-3.00 (m, 5H), 2.44 (d, *J*= 18.3 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 1.82 (s, 3H), 1.80-1.65 (m, 1H), 1.48 (s, 9H), 0.86 (d, *J*= 5.7 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5, 180.8, 172.7, 155.9, 154.5, 147.3, 143.3, 141.5, 135.3, 130.4, 129.2, 127.5, 120.2, 117.4, 116.9, 80.2, 60.7, 60.3, 58.5, 55.9, 55.8, 54.9, 54.4, 50.0, 41.6, 40.3, 28.0, 25.3, 24.0, 18.1, 15.6, 8.5.

ESI-MS m/z: Calcd. for $C_{34}H_{43}N_5O_8$: 649.7. Found $(M+H)^+$: 650.3.

Example 15

Compound **Int-15**



Int-14 Int-15

To a stirred solution of **Int-14** (20.6 g, 31.75 ml) in CH_3CN (159 ml), diisopropylethylamine (82.96 ml, 476.2 ml), methoxymethylene bromide (25.9 ml, 317.5 ml) and dimethylaminopyridine (155 mg, 1.27 ml) were added at 0 °C. The mixture was stirred at 23 °C for 24h. The reaction was quenched at 0 °C with aqueous 0.1N HCl (750 ml) (pH = 5), and extracted with CH_2Cl_2 (2 x 400 ml). The organic phase was dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient hexane:ethyl acetate 4:1 to hexane:ethyl acetate 3:2) to give **Int-15** (17.6 g, 83 %) as a yellow solid.

Rf: 0.38 (hexane:ethyl acetate 3:7).

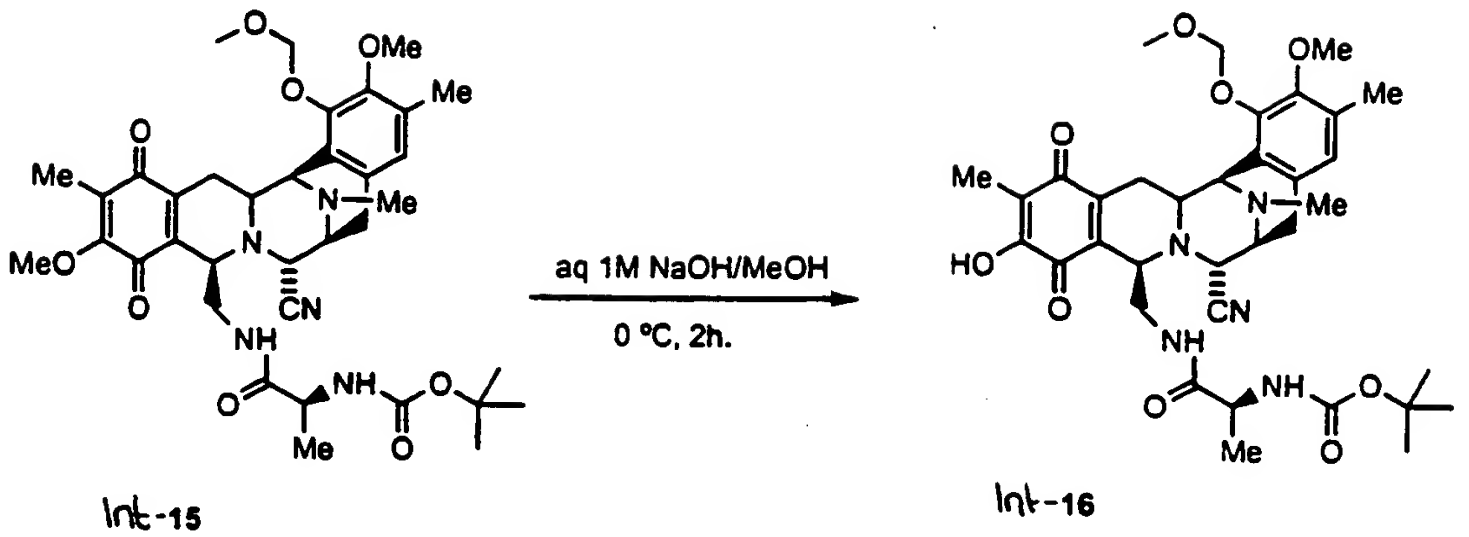
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 5.35 (bs, 1H), 5.13 (s, 2H), 4.50 (bs, 1H), 4.25 (d, *J*= 2.7 Hz, 1H), 4.03 (d, *J*= 2.7 Hz, 1H), 3.97 (s, 3H), 3.84 (bs, 1H), 3.82-3.65 (m, 1H), 3.69 (s, 3H), 3.56 (s, 3H), 3.39-3.37 (m, 1H), 3.20-3.00 (m, 5H), 2.46 (d, *J*= 18 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H), 1.85 (s, 3H), 1.73-1.63 (m, 1H), 1.29 (s, 9H), 0.93 (d, *J*= 5.1 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4, 180.9, 172.4, 155.9, 154.5, 149.0, 148.4, 141.6, 135.1, 131.0, 129.9, 127.6, 124.4, 123.7, 117.3, 99.1, 79.3, 60.7, 59.7, 58.4, 57.5, 56.2, 55.9, 55.0, 54.2, 50.0, 41.5, 39.9, 28.0, 25.2, 24.0, 18.1, 15.6, 8.5.

ESI-MS m/z: Calcd. for $C_{36}H_{47}N_5O_9$: 693.8. Found $(M+H)^+$: 694.3.

Example 16

Compound **Int-16**



Int-15 Int-16

To a flask containing **Int-15** (8 g, 1.5 ml) in methanol (1.6 l) an aqueous solution of 1M sodium hydroxide (3.2 l) was added at 0 °C. The reaction was stirred for 2h at this temperature and then, quenched with 6M HCl to pH = 5. The mixture was extracted with ethyl acetate (3 x 1 l) and the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient $CHCl_3$ to $CHCl_3$:ethyl acetate 2:1) to afford **Int-16** (5.3 mg, 68 %).

Rf: 0.48 (CH_3CN:H_2O 7:3, RP-C18)

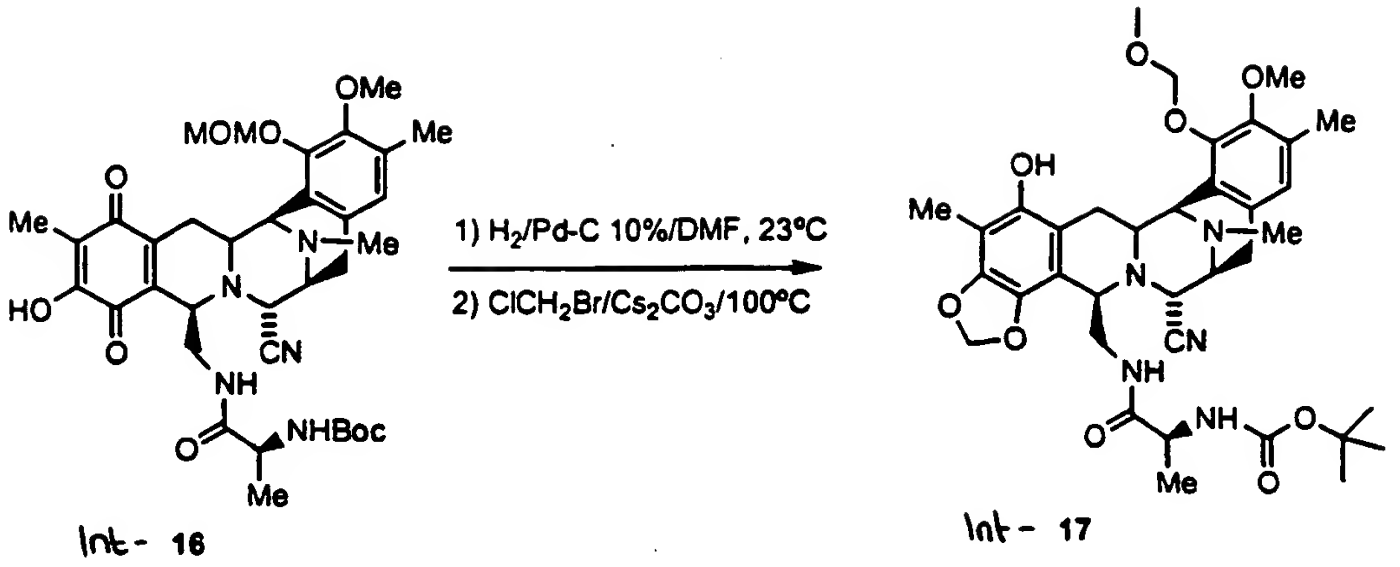
^1H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 5.43 (bs, 1H), 5.16 (s, 2H), 4.54 (bs, 1H), 4.26 (d, *J*= 1.8 Hz, 1H), 4.04 (d, *J*= 2.7 Hz 1H), 3.84 (bs, 1H), 3.80-3.64 (m, 1H), 3.58 (s, 3H), 3.41-3.39 (m, 1H), 3.22-3.06 (m, 5H), 2.49 (d, *J*= 18.6 Hz 1H), 2.35 (s, 3H), 2.30-2.25 (m, 1H), 2.24 (s, 3H), 1.87 (s, 3H), 1.45-1.33 (m, 1H), 1.19 (s, 9H), 1.00 (br d, *J*= 6.6 Hz 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 184.9, 180.9, 172.6, 154.7, 151.3, 149.1, 148.6, 144.7, 132.9, 131.3, 129.8, 124.5, 123.7, 117.3, 116.8, 99.1, 79.4, 59.8, 58.6, 57.7, 56.2, 55.6, 54.9, 54.5, 50.1, 41.6, 40.1, 28.0, 25.3, 24.4, 18.1, 15.7, 8.0.

ESI-MS m/z: Calcd. for $C_{35}H_{45}N_5O_9$: 679.7. Found $(M+H)^+$: 680.3

Example 17

Compound **Int-17**



Int- 16

Int- 17

To a degassed solution of compound **Int-16** (1.8 g, 2.64 ml) in DMF (221 ml) 10 % Pd/C (360 mg) was added and stirred under H_2 (atmospheric pressure) for 45 min. The reaction was filtered through celite under argon, to a flask containing anhydrous Cs_2CO_3 (2.58 g, 7.92 ml). Then, bromochloromethane (3.40 ml 52.8 ml), was added and the tube was sealed and stirred at 100 °C for 2h. The reaction was cooled, filtered through a pad of celite and washed with CH_2Cl_2. The organic layer was concentrated and dried (sodium sulphate) to afford **Int-17** as a brown oil that was used in the next step with no further purification.

Rf: 0.36 (hexane:ethyl acetate 1:5, SiO_2).

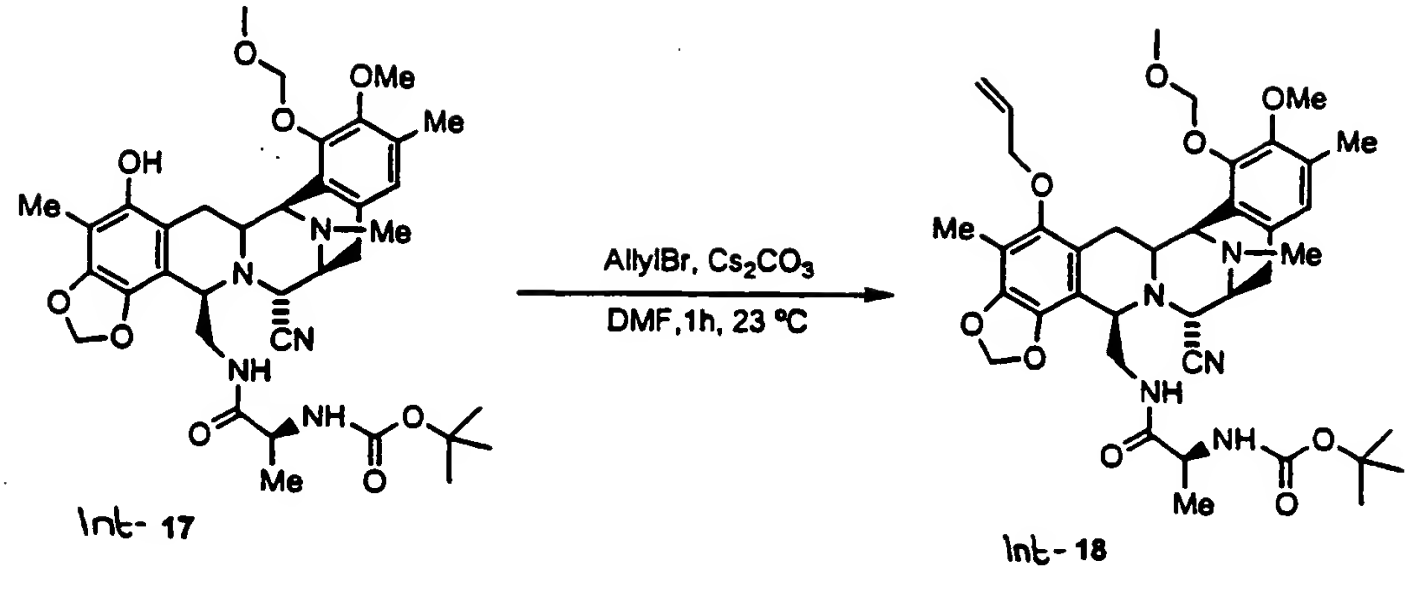
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.05 (bs, 1H), 5.90 (s, 1H), 5.79 (s, 1H), 5.40 (bs, 1H), 5.31-5.24 (m, 2H), 4.67 (d, *J*= 8.1 Hz, 1H), 4.19 (d, *J*= 2.7 Hz, 1H), 4.07 (bs, 1H), 4.01 (bs, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.64-2.96 (m, 5H), 2.65 (d, *J*=18.3 Hz, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 2.04 (s, 3H), 2.01-1.95 (m, 1H), 1.28 (s, 9H), 0.87 (d, *J*= 6.3 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 162.6, 154.9, 149.1, 145.7, 135.9, 130.8, 130.7, 125.1, 123.1, 117.8, 100.8, 99.8, 76.6, 59.8, 59.2, 57.7, 57.0, 56.7, 55.8, 55.2, 49.5, 41.6, 40.1, 36.5, 31.9, 31.6, 29.7, 28.2, 26.3, 25.0, 22.6, 18.2, 15.8, 14.1, 8.8.

ESI-MS m/z: Calcd. for $C_{36}H_{47}N_5O_9$: 693.34. Found $(M+H)^+$: 694.3.

Example 18

Compound **Int-18**



Int- 17 Int- 18

To a flask containing a solution of **Int-17** (1.83 g, 2.65 ml) in DMF (13 ml), Cs_2CO_3 (2.6 g, 7.97 ml), and allyl bromide (1.15 ml, 13.28 ml) were added at 0° C. The resulting mixture was stirred at 23 °C for 1h. The reaction was filtered through a pad of celite and washed with CH_2Cl_2. The organic layer was dried and concentrated (sodium sulphate). The residue was purified by flash column chromatography (SiO_2, $CHCl_3$:ethyl acetate 1:4) to afford **Int-18** (1.08 mg, 56 %) as a white solid.

Rf: 0.36 ($CHCl_3$:ethyl acetate 1:3).

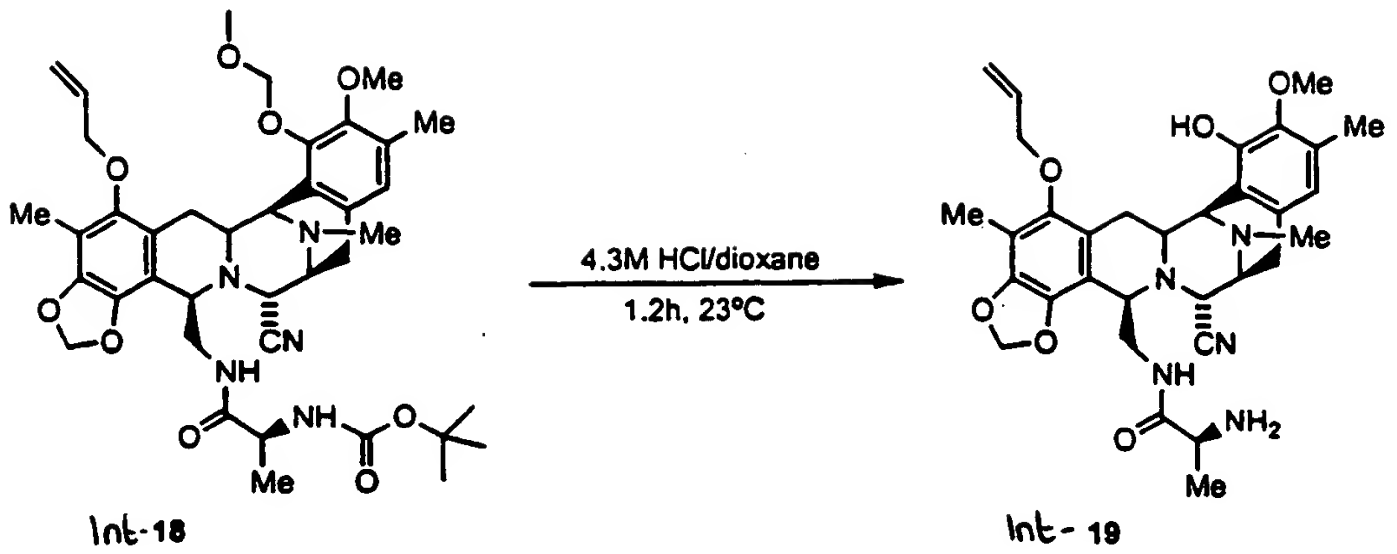
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.27-6.02 (m, 1H), 5.94 (s, 1H), 5.83 (s, 1H), 5.37 (dd, J_1= 1.01 Hz, J_2= 16.8 Hz, 1H), 5.40 (bs, 1H), 5.25 (dd, J_1= 1.0 Hz, J_2= 10.5 Hz, 1H), 5.10 (s, 2H), 4.91 (bs, 1H), 4.25-4.22 (m, 1H), 4.21 (d, J= 2.4 Hz, 1H), 4.14-4.10 (m, 1H), 4.08 (d, J=2.4 Hz, 1H), 4.00 (bs, 1H), 3.70 (s, 3H), 3.59 (s, 3H), 3.56-3.35 (m, 2H), 3.26-3.20 (m, 2H), 3.05-2.96 (dd, J_1= 8.1 Hz, J_2=18 Hz, 1H), 2.63 (d, J=18 Hz, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.09 (s, 3H), 1.91-1.80 (m, 1H), 1.24 (s, 9H), 0.94 (d, J= 6.6 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 154.8, 148.8, 148.6, 148.4, 144.4, 138.8, 133.7, 130.9, 130.3, 125.1, 124.0, 120.9, 117.8, 117.4, 112.8, 112.6, 101.1, 99.2, 73.9, 59.7, 59.3, 57.7, 56.9, 56.8, 56.2, 55.2, 40.1, 34.6, 31.5, 28.1, 26.4, 25.1, 22.6, 18.5, 15.7, 14.0, 9.2.

ESI-MS m/z: Calcd. for $C_{39}H_{51}N_5O_9$: 733.4. Found $(M+H)^+$: 734.4.

Example 19

Compound **Int-19**



Int-18 Int-19

To a solution of **Int-18** (0.1 g, 0.137 ml) in dioxane (2 ml), 4.2M HCl/dioxane (1.46 ml) was added and the mixture was stirred for 1.2h at 23 °C. The reaction was quenched at 0 °C with sat. Aqueous sodium bicarbonate (60 ml) and extracted with ethyl acetate (2x70 ml). The organic layers were dried (sodium sulphate) and concentrated *in vacuo* to afford **Int-19** (267 mg, 95 %) as a white solid that was used in subsequent reactions with no further purification.

Rf: 0.17 (ethyl acetate:methanol 10:1, SiO_2)

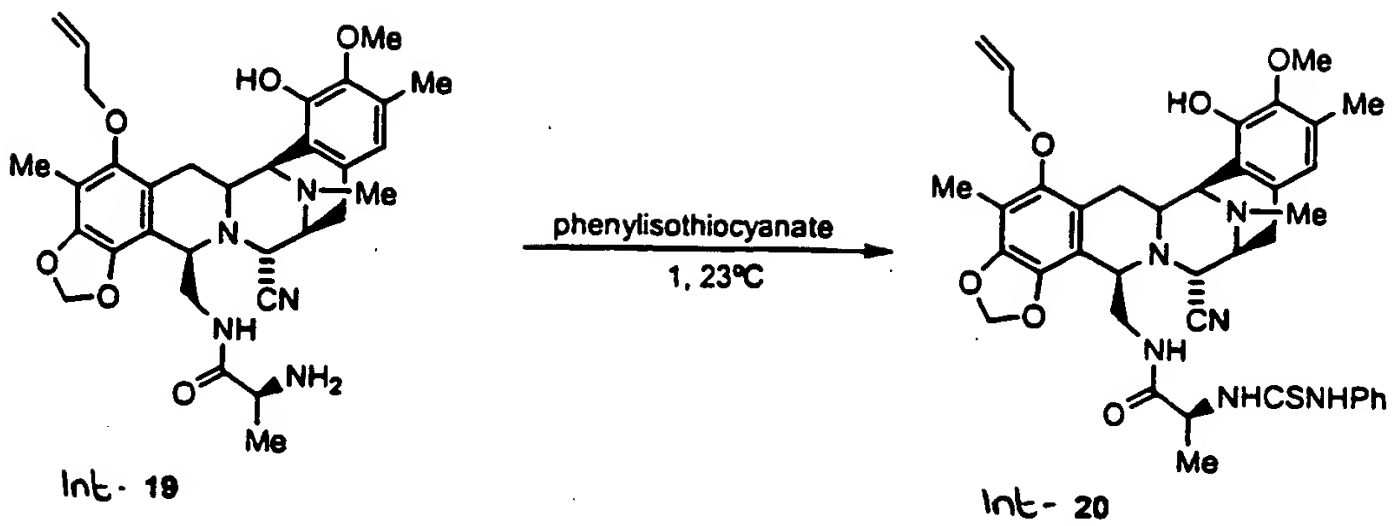
^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6.12-6.00 (m, 1H), 5.94 (s, 1H), 5.86 (s, 1H), 5.34 (dd, *J*= 1.0 Hz, *J*= 17.4 Hz, 1H), 5.25 (dd, *J*= 1.0 Hz, *J*= 10.2 Hz, 1H), 4.18-3.76 (m, 5H), 3.74 (s, 3H), 3.71-3.59 (m, 1H), 3.36-3.20 (m, 4H), 3.01-2.90 (m, 1H), 2.60 (d, *J*= 18.0 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H), 1.97-1.86 (m, 1H), 0.93 (d, *J*= 8.7 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 148.4, 146.7, 144.4, 142.4, 138.9, 133.7, 131.3, 128.3, 120.8, 117.9, 117.4, 113.8, 112.4, 101.1, 74.2, 60.5, 59.1, 56.5, 56.1, 56.3, 56.0, 55.0, 50.5, 41.6, 39.5, 29.5, 26.4, 24.9, 21.1, 15.5, 9.33.

ESI-MS m/z: Calcd. for $C_{32}H_{39}N_5O_6$: 589. Found $(M+H)^+$: 590.

Example 20

Compound **Int-20**



Int- 19 Int- 20

To a solution of **Int-19** (250 mg, 0.42 ml) in CH_2Cl_2 (1.5 ml), phenyl isothiocyanate (0.3 ml, 2.51 ml) was added and the mixture was stirred at 23° C for 1h. The reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, gradient Hexane to 5:1 hexane:ethyl acetate) to afford **Int-20** (270 mg, 87 %) as a white solid.

Rf: 0.56 ($CHCl_3$:ethyl acetate 1:4).

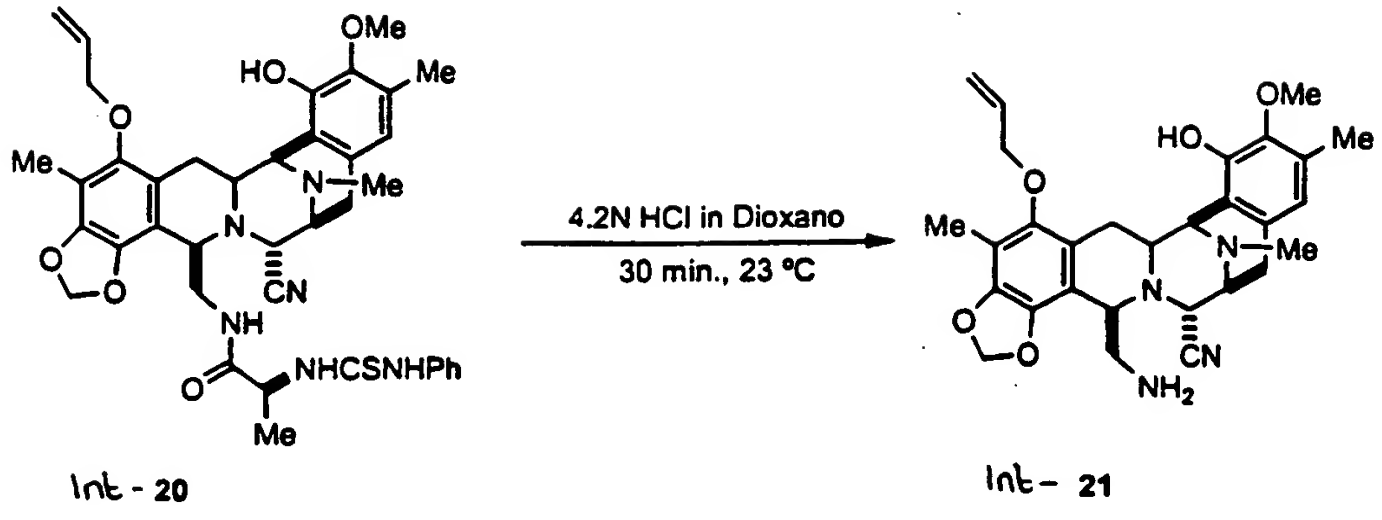
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (bs, 1H), 7.45-6.97 (m, 4H), 6.10 (s, 1H), 6.08-6.00 (m, 1H), 5.92 (s, 1H), 5.89 (s, 1H), 5.82 (s, 1H), 5.40 (dd, *J*= 1.5 Hz, *J*= 17.1 Hz, 1H), 3.38 (bs, 1H), 5.23 (dd, *J*= 1.5 Hz, *J*= 10.5 Hz, 1H), 4.42-4.36 (m, 1H), 4.19-4.03 (m, 5H), 3.71 (s, 3H), 3.68-3.17 (m, 4H), 2.90 (dd, *J*=7.8 Hz, *J*= 18.3 Hz, 1H), 2.57 (d, *J*= 18.3 Hz, 1H), 2.25 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.90 (dd, *J*= 12.3 Hz, *J*= 16.5 Hz, 1H), 0.81 (d, *J*= 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 171.6, 148.6, 146.8, 144.3, 142.7, 138.7, 136.2, 133.6, 130.7, 129.8, 126.6, 124.2, 124.1, 120.9, 120.5, 117.7, 117.4, 116.7, 112.6, 112.5, 101.0, 74.0, 60.6, 59.0, 57.0, 56.2, 56.1, 55.0, 53.3, 41.4, 39.7, 26.3, 24.8, 18.3, 15.5, 9.2.

ESI-MS m/z: Calcd. for $C_{39}H_{44}N_6O_6S$: 724.8 Found $(M+H)^+$: 725.3.

Example 21

Compound **Int-21**



Int - 20 Int - 21

To a solution of **Int-20** (270 mg, 0.37 ml) in dioxane (1 ml), 4.2N HCl/dioxane (3.5 ml) was added and the reaction was stirred at 23 °C for 30 min. Then, ethyl acetate (20 ml) and H_2O (20 ml) were added and the organic layer was decanted. The aqueous phase was basified with saturated aqueous sodium bicarbonate (60 ml) (pH = 8) at 0 °C and then, extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried (sodium sulphate), and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, ethyl acetate:methanol 5:1) to afford compound **Int-21** (158 mg, 82%) as a white solid.

Rf: 0.3 (ethyl acetate:methanol 1:1).

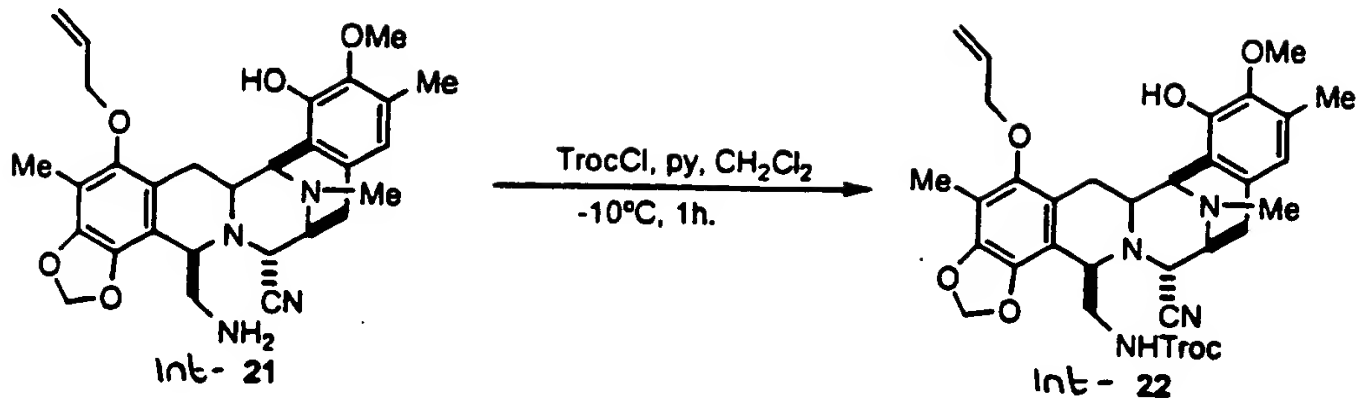
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (s, 1H), 6.12-6.03 (m, 1H), 5.91 (s, 1H), 5.85 (s, 1H), 5.38 (dd, J_1= 1.2 Hz, J_2= 17.1 Hz, 1H), 5.24 (dd, J_1= 1.2 Hz, J_2= 10.5 Hz, 1H), 4.23-4.09 (m, 4H), 3.98 (d, J= 2.1 Hz, 1H), 3.90 (bs, 1H), 3.72 (s, 3H), 3.36-3.02 (m, 5H), 2.72-2.71 (m, 2H), 2.48 (d, J= 18.0 Hz, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H), 1.85 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H)).

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 146.7, 144.4, 142.8, 138.8, 133.8, 130.5, 128.8, 121.5, 120.8, 118.0, 117.5, 116.9, 113.6, 112.2, 101.1, 74.3, 60.7, 59.9, 58.8, 56.6, 56.5, 55.3, 44.2, 41.8, 29.7, 26.5, 25.7, 15.7, 9.4.

ESI-MS m/z: Calcd. for $C_{29}H_{34}N_4O_5$: 518.3. Found $(M+H)^+$: 519.2.

Example 22

Compound **Int-22**



To a solution of **Int-21** (0.64 g, 1.22 ml) in CH_2Cl_2 (6.13 ml), pyridine (0.104 ml, 1.28 ml) and 2,2,2-trichloroethyl chloroformate (0.177 ml, 1.28 ml) were added at -10 °C. The mixture was stirred at this temperature for 1h and then, the reaction was quenched by addition of 0.1N HCl (10 ml) and extracted with CH_2Cl_2 (2 x 10 ml). The organic layer was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, (hexane:ethyl acetate 1:2) to afford **Int-22** (0.84 g, 98%) as a white foam solid.

Rf: 0.57 (ethyl acetate:methanol 5:1).

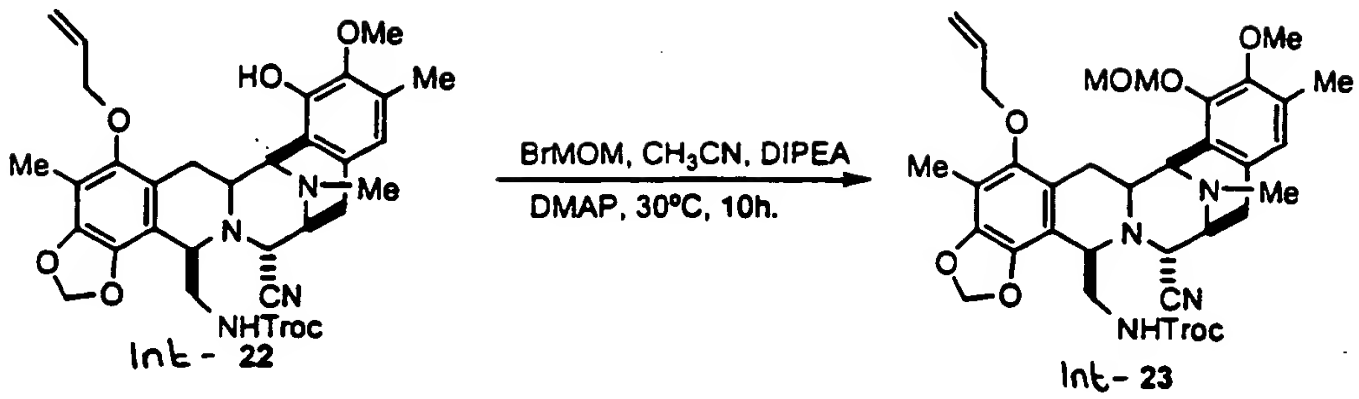
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 6.10-6.00 (m, 1H), 6.94 (d, J= 1.5 Hz, 1H), 5.87 (d, J= 1.5 Hz, 1H), 5.73 (bs, 1H), 5.37 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.26 (dq, J_1= 1.8 Hz, J_2= 10.2 Hz, 1H), 4.60 (d, J= 12 Hz, 1H), 4.22-4.10 (m, 4H), 4.19 (d, J= 12 Hz, 1H), 4.02 (m, 2H), 3.75 (s, 3H), 3.37-3.18 (m, 5H), 3.04 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.63 (d, J= 18 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H), 1.85 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 148.5, 146.7, 144.5, 142.8, 139.0, 133.8, 130.7, 128.7, 121.3, 120.8, 117.8, 117.7, 116.8, 112.7, 101.2, 77.2, 74.3, 60.7, 59.9, 57.0, 56.4, 55.3, 43.3, 41.7, 31.6, 26.4, 25.3, 22.6, 15.9, 14.1, 9.4.

ESI-MS m/z: Calcd. for $C_{32}H_{35}Cl_3N_4O_7$: 694.17. Found $(M+H)^+$: 695.2.

Example 23

Compound **Int-23**



To a solution of **Int-22** (0.32 g, 0.46 ml) in CH_3CN (2.33 ml), diisopropylethylamine (1.62 ml, 9.34 ml), bromomethyl methyl ether (0.57 ml, 7.0 ml) and dimethylaminopyridine (6 mg, 0.046 ml) were added at 0 °C. The mixture was heated at 30 °C for 10h. Then, the reaction was diluted with dichloromethane (30 ml) and poured in an aqueous solution of HCl at pH = 5 (10 ml). The organic layer was dried over sodium sulphate and the solvent was eliminated under reduced pressure to give a residue which was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 2:1) to afford **Int-23** (0.304 g, 88%) as a white foam solid.

Rf: 0.62 (hexane:ethyl acetate 1:3).

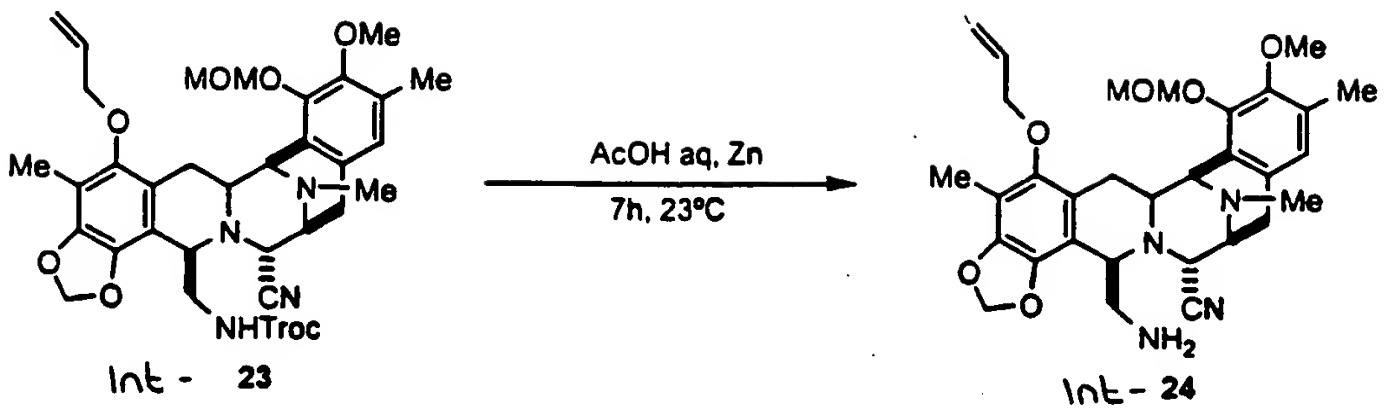
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 6.10 (m, 1H), 5.94 (d, J= 1.5 Hz, 1H), 5.88 (d, J= 1.5 Hz, 1H), 5.39 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.26 (dq, J_1= 1.8 Hz, J_2= 10.2 Hz, 1H), 5.12 (s, 2H), 4.61 (d, J= 12 Hz, 1H), 4.55 (t, J= 6.6 Hz, 1H), 4.25 (d, J= 12 Hz, 1H), 4.22-4.11 (m, 4H), 4.03 (m, 2H), 3.72 (s, 3H), 3.58 (s, 3H), 3.38-3.21 (m, 5H), 3.05 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.65 (d, J= 18 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H), 1.79 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 148.6, 148.4, 144.5, 139.0, 133.6, 130.6, 130.1, 125.07, 124.7, 124.0, 121.1, 117.7, 112.6, 101.2, 99.2, 77.2, 74.4, 74.1, 59.8, 59.8, 57.7, 57.0, 56.8, 56.68, 55.3, 43.2, 41.5, 26.4, 25.2, 15.9, 9.3.

ESI-MS m/z: Calcd. for $C_{34}H_{39}Cl_3N_4O_8$: 738.20. Found $(M+H)^+$: 739.0.

Example 24

Compound **Int-24**



Int - 23 Int - 24

To a suspension of **Int-23** (0.304 g, 0.41 ml) in 90% aqueous acetic acid (4 ml), powder zinc (0.2 g, 6.17 ml) was added and the reaction was stirred for 7 hour at 23 °C. The mixture was filtered through a pad of celite which was washed with CH_2Cl_2. The organic layer was washed with an aqueous sat. solution of sodium bicarbonate (pH = 9) (15 ml) and dried over sodium sulphate. The solvent was eliminated under reduced pressure to give **Int-24** (0.191 g, 83%) as a white solid.

Rf: 0.3 (ethyl acetate:methanol 5:1).

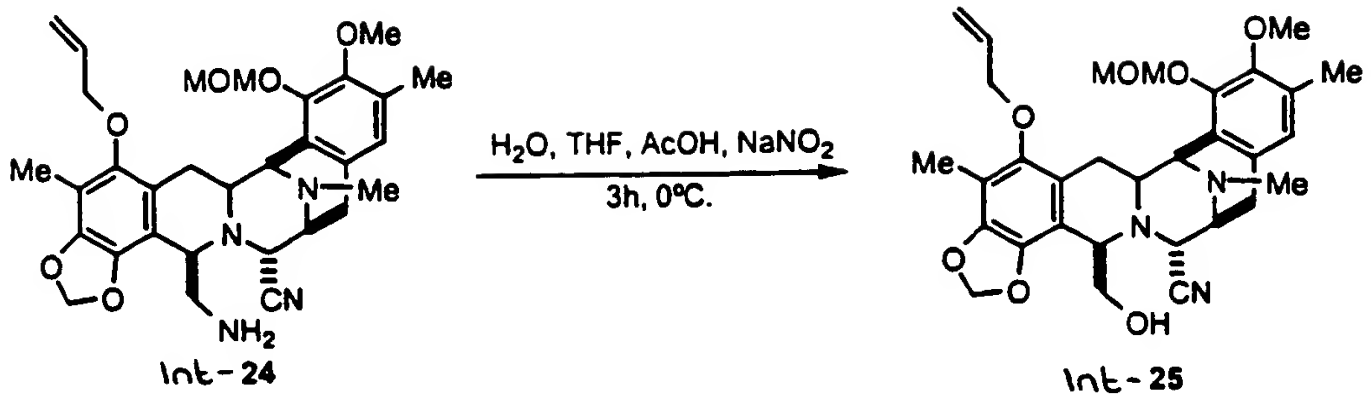
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.09 (m, 1H), 5.90 (d, J= 1.5 Hz, 1H), 5.83 (d, J= 1.5 Hz, 1H), 5.39 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.25 (dq, J_1= 1.5 Hz, J_2= 10.2 Hz, 1H), 5.10 (s, 2H), 4.22-4.09 (m, 3H), 3.98 (d, J= 2.4 Hz, 1H), 3.89 (m, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 3.37-3.17 (m, 3H), 3.07 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.71 (m, 2H), 2.48 (d, J= 18 Hz, 1H), 2.33 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.80 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 148.2, 144.3, 138.7, 133.7, 130.7, 129.9, 125.0, 123.9, 121.3, 117.9, 117.5, 113.6, 112.0, 101.0, 99.2, 74.0, 59.8, 59.7, 58.8, 57.6, 57.0, 56.2, 55.2, 44.2, 41.5, 31.5, 26.4, 25.6, 22.5, 16.7, 14.0, 9.2.

ESI-MS m/z: Calcd. for $C_{31}H_{38}N_4O_6$: 562.66. Found $(M+H)^+$: 563.1.

Example 25

Compound **Int-25**



To a solution of **Int-24** (20 mg, 0.035 ml), in H_2O (0.7 ml) and THF (0.7 ml), $NaNO_2$ (12 mg, 0.17 ml) and 90% aqueous AcOH (0.06 ml) were added at 0 °C and the mixture was stirred at 0 °C for 3h. After dilution with CH_2Cl_2 (5 ml), the organic layer was washed with water (1 ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 2:1) to afford **Int-25** (9.8 mg, 50%) as a white solid.

Rf: 0.34 (hexane:ethyl acetate 1:1).

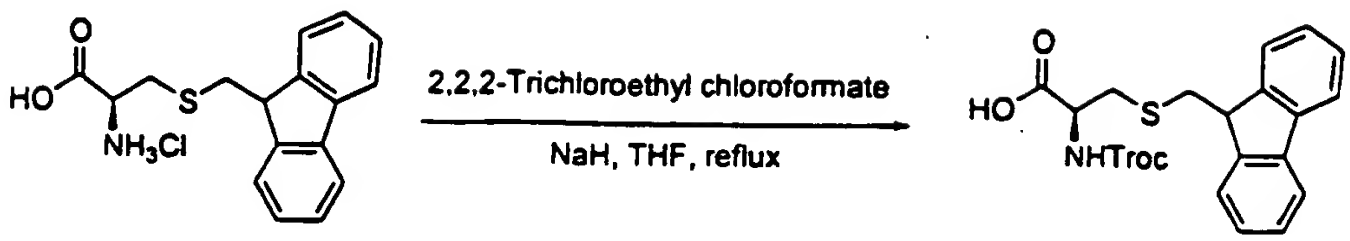
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.11 (m, 1H), 5.92 (d, J= 1.5 Hz, 1H), 5.87 (d, J= 1.5 Hz, 1H), 5.42 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.28 (dq, J_1= 1.5 Hz, J_2= 10.2 Hz, 1H), 5.12 (s, 2H), 4.26-4.09 (m, 3H), 4.05 (d, J= 2.4 Hz, 1H), 3.97 (t, J= 3.0 Hz, 1H), 3.70 (s, 3H), 3.67-3.32 (m, 4H), 3.58 (s, 3H), 3.24 (dd, J_1= 2.7 Hz, J_2= 15.9 Hz, 1H), 3.12 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.51 (d, J= 18 Hz, 1H), 2.36 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H), 1.83 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 148.4, 138.9, 133.7, 131.1, 129.4, 125.1, 123.9, 120.7, 117.6, 117.5, 113.2, 112.3, 101.1, 99.2, 74.0, 63.2, 59.8, 59.7, 57.9, 57.7, 57.0, 56.5, 55.2, 41.6, 29.6, 26.1, 25.6, 22.6, 15.7, 9.2.

ESI-MS m/z: Calcd. for $C_{31}H_{37}N_3O_7$: 563.64. Found $(M+H)^+$: 564.1.

Example 29

Compound **Int-29**



Int - 29

The starting material (2.0 g, 5.90 ml) was added to a suspension of sodium hydride (354 mg, 8.86 ml) in THF (40 ml) at 23 °C, following the suspension was treated with allyl chloroformate (1.135 ml, 8.25 ml) at 23 °C and then refluxed for 3 hours. The suspension was cooled, filtered off, the solid washed with ethyl acetate (100 ml), and the filtrate was concentrated. The oil crude was ground with hexane (100 ml) and kept at 4°C overnight. After, the solvent was decanted and the light yellow slurry was treated with CH_2Cl_2 (20 ml), and precipitated with hexane (100 ml). After 10 minutes, the solvent was decanted again. The operation was repeated until appearing a white solid. The white solid was filtered off and dried to afford compound **Int-29** (1.80 g, 65%) as a white solid.

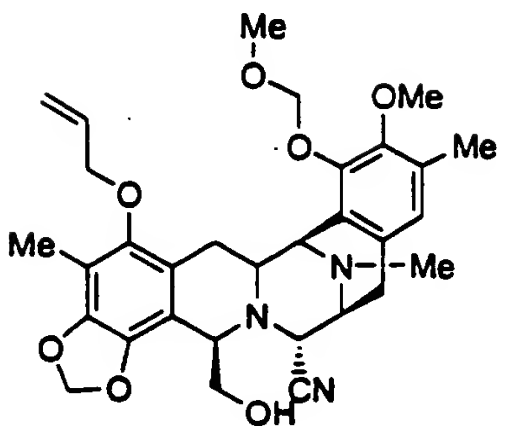
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J*= 7.5 Hz, 2H), 7.62 (d, *J*= 6.9 Hz, 2H), 7.33 (t, *J*= 7.5 Hz, 2H), 7.30 (t, *J*= 6.3 Hz, 2H), 5.71 (d, *J*= 7.8 Hz, 1H), 4.73 (d, *J*= 7.8 Hz, 2H), 4.59 (m, 1H), 4.11 (t, *J*= 6.0 Hz, 1H), 3.17 (dd, *J*= 6.0 Hz, *J*= 2.7 Hz, 2H), 3.20 (dd, *J*= 5.4 Hz, *J*= 2.1 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.6, 152.7, 144.0, 139.7, 137.8, 126.0, 125.6, 123.4, 118.3, 73.4, 52.4, 45.5, 35.8, 33.7.

ESI-MS m/z: Calcd.. for $C_{20}H_{18}Cl_3NO_4S$: 474.8. Found $(M+Na)^+$: 497.8

Example 30

Compound **Int-30**



A mixture of compound **Int-25** (585 mg, 1.03 ml) and compound **Int-29** (1.47 mg, 3.11 ml) were azeotroped with anhydrous toluene (3 x 10 ml). To a solution of **Int-25** and **Int-29** in anhydrous CH_2Cl_2 (40 ml) was added DMAP (633 mg, 5.18 ml) and EDC·HCl (994 mg, 5.18 ml) at 23 °C. The reaction mixture was stirred at 23 °C for 3 hours. The mixture was partitioned with saturated aqueous solution of sodium bicarbonate (50 ml) and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (50 ml). The combined organic layers were dried over sodium sulphate, filtered and concentrated. The crude was purified by flash column chromatography (ethyl acetate/hexane 1:3) to obtain **Int-30** (1.00 g, 95%) as a pale cream yellow solid.

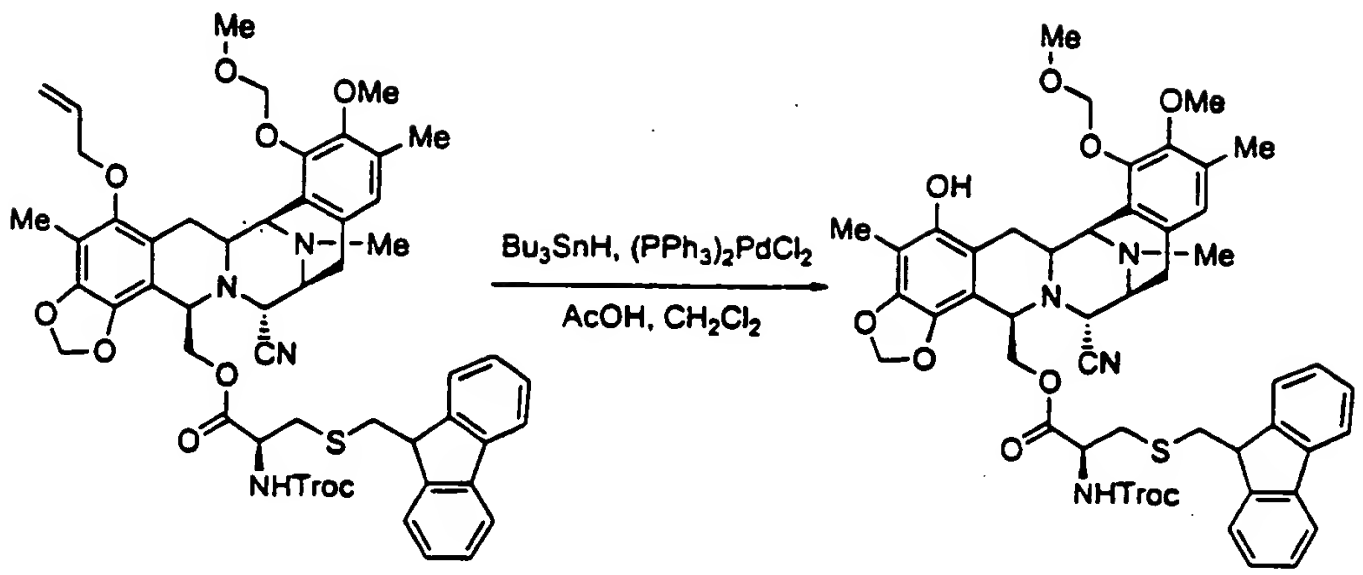
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.52 (m, 2H), 7.38 (m, 2H), 7.28 (m, 2H), 6.65 (s, 1H), 6.03 (m, 1H), 5.92 (d, *J*= 1.5 Hz, 1H), 5.79 (d, *J*= 1.5 Hz, 1H), 5.39 (m, 1H), 5.29 (dq, *J*= 10.3 Hz, *J*= 1.5 Hz, 1H), 5.10 (s, 2H), 4.73 (d, *J*= 11.9 Hz, 1H), 4.66 (d, *J*= 11.9 Hz, 1H), 4.53 (m, 1H), 4.36-3.96 (m, 9H), 3.89 (t, *J*= 6.4 Hz, 1H), 3.71 (s, 3H), 3.55 (s, 3H), 3.33 (m, 1H), 3.20 (m, 2H), 2.94 (m, 3H), 2.59 (m, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.02 (s, 3H), 1.83 (dd, *J*= 16.0 Hz, *J*= 11.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 169.7, 154.0, 148.8, 148.4, 145.7, 144.5, 140.9, 139.0, 133.7, 130.9, 130.6, 127.6, 127.0, 124.8, 124.6, 124.1, 120.8, 119.9, 118.2, 117.7, 117.3, 112.7, 112.1, 101.3, 99.2, 74.7, 73.9, 64.4, 59.8, 57.7, 57.0, 56.8, 55.4, 53.3, 46.7, 41.4, 36.5, 34.7, 31.5, 26.4, 24.9, 22.6, 15.7, 14.0, 9.1.

ESI-MS m/z: Calcd.. for $C_{51}H_{53}Cl_3N_4O_{10}S$: 1020.4. Found $(M+H)^+$: 1021.2

Example 31

Compound **Int-31**



Int-30 Int-31

To a solution of **Int-30** (845 mg, 0.82 ml), acetic acid (500 mg, 8.28 ml) and $(PPh_3)_2PdCl_2$ (29 mg, 0.04 ml) in anhydrous CH_2Cl_2 20 ml at 23 °C was added, dropwise, Bu_3SnH (650 mg, 2.23 ml). The reaction mixture was stirred at this temperature for 15 min., bubbling was. The crude was quenched with water (50ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried over sodium sulphate, filtered and concentrated. The crude was purified by flash column chromatography (ethyl acetate/hexane in gradient from 1:5 to 1:3) to obtain compound **Int-31** (730 mg, 90%) as a pale cream yellow solid.

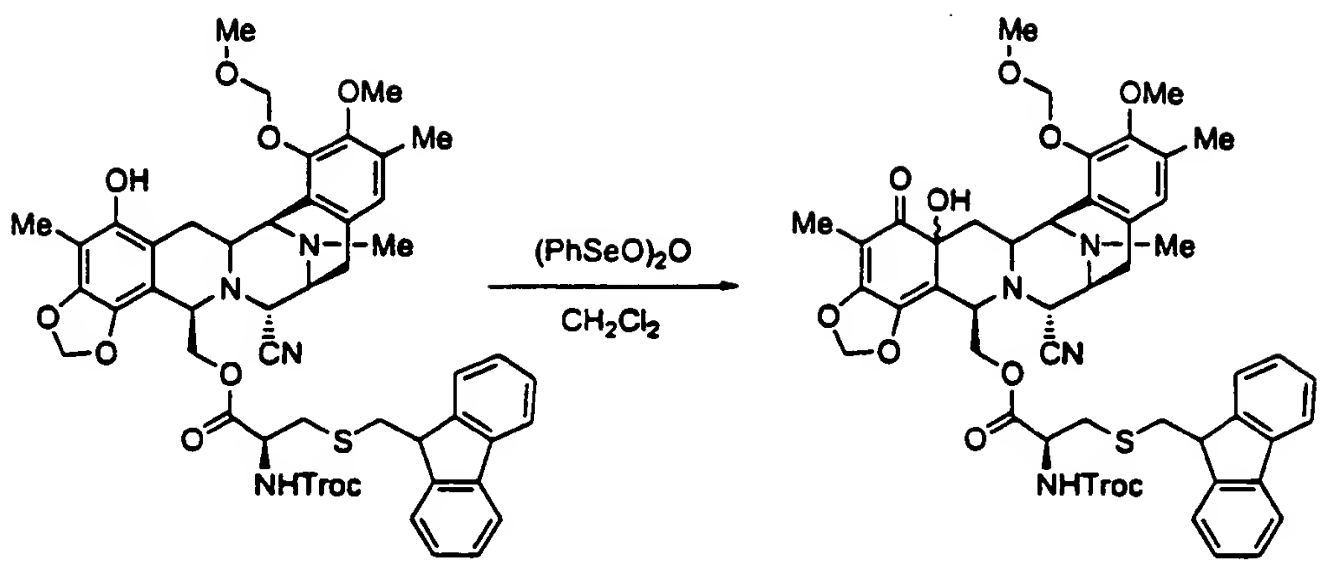
^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.56 (m, 2H), 7.37 (m, 2H), 7.30 (m, 2H), 6.65 (s, 1H), 5.89 (s, 1H), 5.77 (s, 1H), 5.74 (s, 1H), 5.36 (d, *J*= 5.9 Hz, 1H), 5.32 (d, *J*= 5.9 Hz, 1H), 5.20 (d, *J*= 9.0, 1H), 4.75 (d, *J*= 12.0 Hz, 1H), 4.73 (m, 1H), 4.48 (d, *J*= 11.9 Hz, 1H), 4.08 (m, 4H), 3.89 (m, 1H), 3.86, (t, *J*= 6.2 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.38 (m, 1H), 3.25 (m, 1H), 3.02-2.89 (m, 4H), 2.67 (s, 1H), 2.61 (s, 1H), 2.51 (dd, *J*= 14.3 Hz, *J*= 4.5 Hz, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 1.95 (s, 3H), 1.83 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.2, 152.5, 148.1, 146.2, 144.4, 144.3, 143.3, 139.6, 134.6, 129.7, 129.6, 126.2, 125.6, 123.4, 123.3, 121.6, 118.5, 116.3, 110.7, 110.2, 105.1, 99.4, 98.5, 75.2, 73.3, 61.7, 58.4, 57.9, 56.3, 56.1, 55.1, 54.7, 53.9, 51.9, 45.2, 40.1, 35.6, 33.3, 24.8, 23.3., 14.5, 7.3.

ESI-MS m/z: Calcd.. for $C_{48}H_{49}Cl_3N_4O_{10}S$: 980.3. Found $(M+H)^+$: 981.2

Example 32

Compound **Int-32**



Int- 31 Int- 32

To a solution of **Int-31** (310 mg, 0.32 ml), in anhydrous CH_2Cl_2 (15 ml) at -10 °C was added a solution of benzeneseleninic anhydride 70 % (165 mg, 0.32 ml), in anhydrous CH_2Cl_2 (7 ml), *via* cannula, keeping the temperature at -10 °C. The reaction mixture was stirred at -10 °C for 5 min. A saturated solution of sodium bicarbonate (30 ml) was added at this temperature. The aqueous layer was washed with more CH_2Cl_2 (40 ml). The organic layers were dried over sodium sulphate, filtered and concentrated. The crude was purified by flash column chromatography (ethyl acetate/hexane in gradient from 1:5 to 1:1) to obtain **Int-32** (287 mg, 91%, HPLC: 91.3%) as a pale cream yellow solid and as a mixture of two isomers (65:35) which were used in the next step.

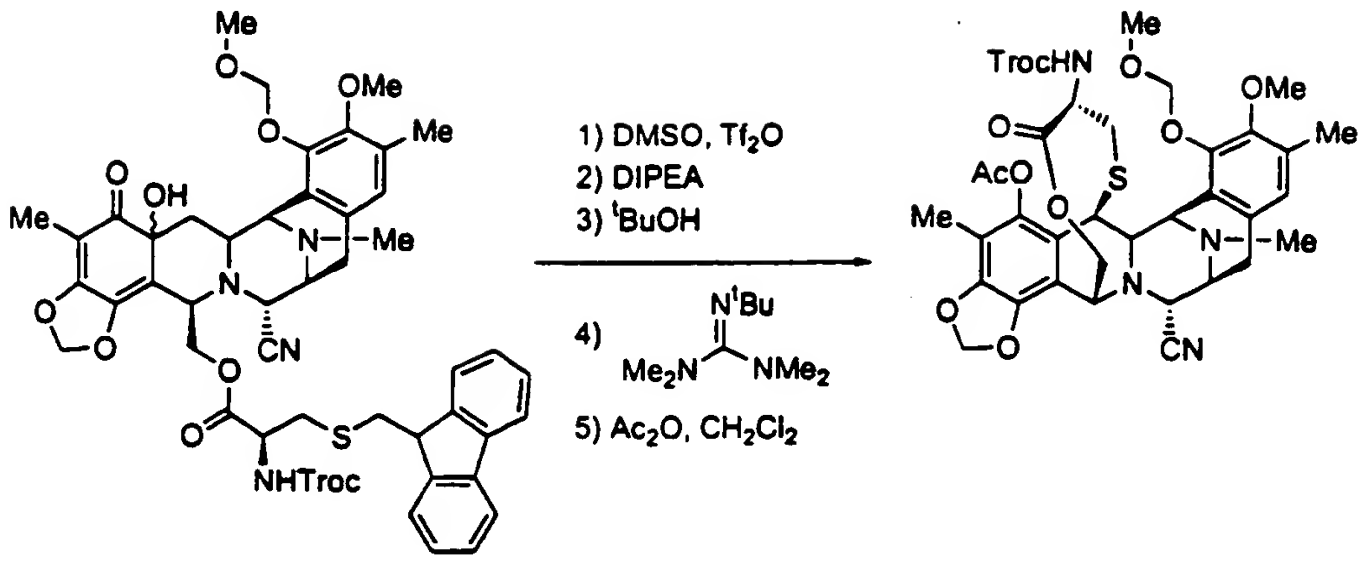
^{1}H-NMR (300 MHz, $CDCl_3$): δ (Mixture of isomers) 7.76 (m, 4H), 7.65 (m, 4H), 7.39 (m, 4H), 7.29 (m, 4H), 6.62 (s, 1H), 6.55 (s, 1H), 5.79-5.63 (m, 6H), 5.09 (s, 1H), 5.02 (d, *J*= 6.0 Hz, 1H), 4.99 (d, *J*= 6.0 Hz, 1H), 4.80-4.63 (m, 6H), 4.60 (m, 1H), 4.50 (m, 1H), 4.38 (d, *J*= 12.8 Hz, *J*= 7.5 Hz, 1H), 4.27 (dd, *J*= 12.8 Hz, *J*= 7.5 Hz, 1H), 4.16-3.90 (m, 10H), 3.84 (s, 3H), 3.62 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 3.33-2.83 (m, 14H), 2.45-2.18 (m, 2H), 2.21 (s, 6H), 2.17 (s, 6H), 1.77 (s, 6H), 1.67 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (Mixture of isomers) 168.6, 168.4, 158.6, 154.8, 152.8, 152.5, 147.3, 147.2, 146.8, 144.1, 144.0, 140.8, 139.7, 137.1, 129.8, 129.3, 128.4, 128.7, 126.5, 125.5, 123.7, 123.6, 123.5, 123.4, 122.2, 121.3, 118.3, 115.8, 115.5, 110.2, 106.9, 103.5, 103.2, 100.1, 99.6, 97.9, 97.7, 93.8, 73.4, 70.9, 69.2, 64.9, 62.5, 59.3, 58.9, 58.4, 56.7, 56.3, 56.2, 55.4, 55.2, 55.1, 54.9, 54.7, 54.3, 54.1, 53.8, 52.8, 45.5, 40.5, 40.0, 39.8, 35.8, 35.5, 33.9, 33.7, 30.1, 28.8, 24.2, 24.1, 21.2, 14.5, 14.4, 12.7, 6.0, 5.7.

ESI-MS m/z: Calcd.. for $C_{48}H_{49}Cl_3N_4O_{11}S$: 996.3. Found $(M+H)^+$: 997.2

Example 33

Compound **Int-33**



Int- 32 Int- 33

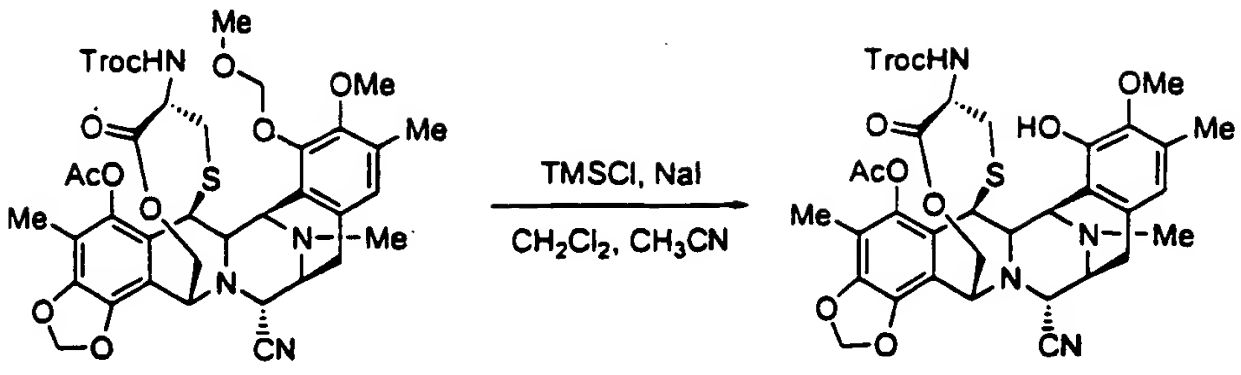
The reaction flask was flamed twice, purged vacuum/Argon several times and kept under Argon atmosphere for the reaction. To a solution of DMSO (39.1 ml, 0.55 ml, 5 equivalents.) in anhydrous CH_2Cl_2 (4.5 ml) was dropwise added triflic anhydride (37.3 ml, 0.22 ml, 2 equivalents.) at -78 °C . The reaction mixture was stirred at -78 °C for 20 minutes, then a solution of **Int-32** (110 mg, 0.11 ml, HPLC: 91.3%) in anhydrous CH_2Cl_2 (1 ml, for the main addition and 0.5 ml for wash) at -78 °C was added, *via* cannula. During the addition the temperature was kept at -78 °C in both flasks and the colour changed from yellow to brown. The reaction mixture was stirred at -40 °C for 35 minutes. During this period of time the solution was turned from yellow to dark green. After this time, $^i Pr_2NEt$ (153 ml, 0.88 ml, 8 equivalents.) was dropwise added and the reaction mixture was kept at 0 °C for 45 minutes, the colour of the solution turned to brown during this time. Then t-butanol (41.6 ml, 0.44 ml, 4 equivalents.) and 2-^{t}Butyl-1,1,3,3-tetramethylguanidine (132.8 ml, 0.77 ml, 7 equivalents.) were dropwise added and the reaction mixture was stirred at 23 °C for 40 minutes. After this time, acetic anhydride (104.3 ml, 1.10 ml, 10 equivalents.) was dropwise added and the reaction mixture was kept at 23 °C for 1 hour more. Then the reaction mixture was diluted with CH_2Cl_2 (20ml) and washed with aqueous saturated solution of NH_4Cl (50ml), sodium

bicarbonate (50ml), and sodium chloride (50ml). The combined organic layers were dried over sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane gradient from 1:3 to 1:2) to afford compound **Int-33** (54 mg, 58%) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.09 (s, 1H), 5.99 (s, 1H), 5.20 (d, *J*= 5.8 Hz, 1H), 5.14 (d, *J*= 5.3 Hz, 1H), 5.03 (m, 1H), 4.82 (d, *J*= 12.2, 1H), 4.63 (d, *J*= 12.0 Hz, 1H), 4.52 (m, 1H), 4.35-4.17 (m, 4H), 3.76 (s, 3H), 3.56 (s, 3H), 3.45 (m, 2H), 2.91 (m, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H), 2.12 (m, 2H), 2.03 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.5, 167.2, 152.7, 148.1, 147.1, 144.5, 139.6, 139.1, 130.5, 129.0, 123.7, 123.5, 123.3, 118.8, 116.5, 112.1, 100.6, 97.8, 73.3, 60.5, 59.4, 59.2, 58.3, 57.6, 57.4, 56.1, 53.3, 53.1, 40.6, 40.0, 31.0, 22.2, 18.9, 14.4, 8.1.
ESI-MS m/z: Calcd.. for $C_{36}H_{39}Cl_3N_4O_{11}S$: 842.1. Found $(M+H)^+$: 843.1

Example 34

Compound **Int-34**



Int- 33 Int- 34

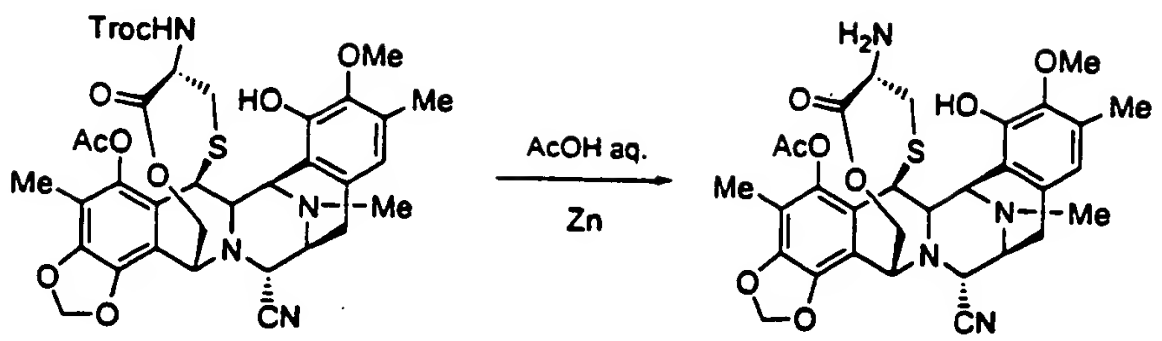
To a solution of **Int-33** (12 mg, 0.014 ml)in dry dichloromethane (1.2 ml) and HPLC grade acetonitrile (1.2 ml) was added at 23 °C sodium iodide (21 mg, 0.14 ml) and freshly distilled (over calcium hydride at atmospheric pressure) trimethylsilyl chloride (15.4 mg, 0.14 ml). The reaction mixture turned to orange colour. After 15 min the solution was diluted with dichloromethane (10 ml) and was washed with a freshly aqueous saturated solution of $Na_2S_2O_4$ (3 x 10 ml). The organic layer was dried over sodium sulphate, filtered and concentrated. It was obtained compound **Int-34** (13 mg, quantitative) as pale yellow solid which was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ.6.85 (s, 1H), 6.09 (s, 1H), 5.99 (s, 1H), 5.27 (d, *J*= 5.8 Hz, 1H), 5.14 (d, *J*= 5.3 Hz, 1H), 5.03 (d, *J*= 11.9 Hz, 1H), 4.82 (d, *J*= 12.2, 1H), 4.63 (d, *J*= 13.0 Hz, 1H), 4.52 (m, 1H), 4.34 (m, 1H), 4.27 (bs, 1H), 4.18 (m, 2H), 3.76 (s, 3H), 3.56 (s, 3H), 3.44 (m, 1H), 3.42 (m, 1H), 2.91 (m, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H), 2.03 (s, 3H).

ESI-MS m/z: Calcd.. for $C_{34}H_{35}N_4O_{10}S$: 798.1. Found $(M+H)^+$: 799.1

Example 35

Compound **Int-35**



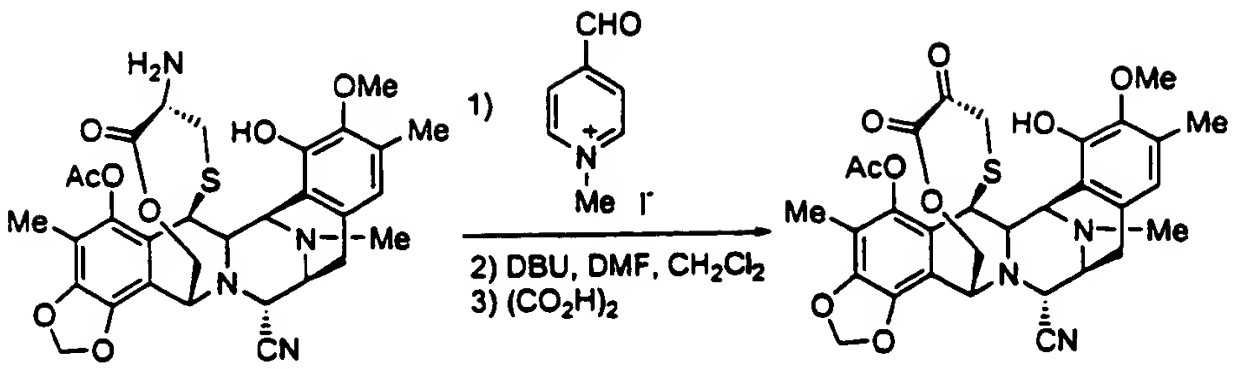
Int- 34 Int-35

To a solution of **Int-34** (13 mg, 0.016 ml) in a mixture of acetic acid/H_2O (90:10, 1 ml) was added powder Zinc (5.3 mg, 0.081 ml) at 23 °C. The reaction mixture was heated at 70 °C for 6 h. After this time, was cooled to 23 °C, diluted with CH_2Cl_2 (20 ml) and washed with aqueous saturated solution of sodium bicarbonate (15 ml) and aqueous solution of Et_3N (15 ml). The organic layer was dried over sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography with Silica-NH_2 (eluent: ethyl acetate/hexane gradient from 0:100 to 50:50) to afford compound **Int-35** (6.8 mg, 77% for two steps) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.51 (s, 1H), 6.03 (dd, *J*= 1.3 Hz, *J*= 26.5 Hz, 2H), 5.75 (bs, 1H), 5.02 (d, *J*= 11.6 Hz, 1H), 4.52 (m, 1H), 4.25 (m, 2H), 4.18 (d, *J*= 2.5 Hz, 1H), 4.12 (dd, *J*= 1.9 Hz, *J*= 11.5 Hz, 1H), 3.77 (s, 3H), 3.40 (m, 2H), 3.26 (t, *J*= 6.4 Hz, 1H), 2. 88 (m, 2H), 2.30-2.10 (m, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H), 2.02 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.1, 168.4, 147.8, 145.4, 142.9, 140.8, 140.1, 131.7, 130.2, 129.1, 128.3, 120.4, 118.3, 117.9, 113.8, 111.7, 101.7, 61.2, 59.8, 59.2, 58.9, 54.4, 53.8, 54.4, 41.3, 41.5, 34.1, 23.6, 20.3, 15.5, 9.4.
ESI-MS m/z: Calcd.. for $C_{31}H_{34}N_4O_8S$: 622.7. Found $(M+H)^+$: 623.2.

Example 36

Compound **Int-36**



Int- 35 Int - 36

A solution of N-methyl pyridine-4-carboxaldehyde iodide (378 mg, 1.5 mmol) in anhydrous DMF (5.8 mL) was treated with anhydrous toluene (2 x 10 mL) to eliminate the amount of water by azeotropic removal of the toluene. A solution of 35 (134 mg, 0.21 mmol), previously treated with anhydrous toluene (2 x 10 mL), in anhydrous CH2Cl2 (distilled over CaH2, 7.2 mL) was added, via cannula, at 23 oC to this orange solution. The reaction mixture was stirred at 23 °C for 4 hours. After this time DBU (32.2 L, 0.21mmol) was dropwise added at 23 °C and it was stirred for 15 minutes at 23 °C. A freshly aqueous saturated solution of oxalic acid (5.8 mL) was added to the reaction mixture and was stirred for 30 minutes at 23 °C. Then the reaction mixture was cooled to 0 °C and NaHCO3 was portionwise added followed by addittion of aqueous saturated solution of NaHCO3. The mixture was extracted with Et2O. K2CO3 was added to the aqueous layer and it was extrated with Et2O. The combined organic layers were dried over MgSO4 and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (AcOEt/hexane from 1/3 to 1/1) to afford compound 36 (77 mg, 57%) as pale yellow solid. 1H-NMR (300 MHz, CDCl3): 6.48 (s, 1H), 6.11 (d, J= 1.3 Hz, 1H), 6.02 (d, J= 1.3 Hz, 1H), 5.70 (bs, 1H), 5.09 (d, J= 11.3 Hz, 1H), 4.66 (bs, 1H), 4.39 (m, 1H), 4.27 (d, J= 5.6 Hz, 1H), 4.21 (d, J= 10.5 Hz, 1H), 4.16 (d, J= 2.6 Hz, 1H), 3.76 (s, 3H), 3.54 (d, J= 5.1 Hz, 1H), 3.42 (d, J= 8.5 Hz, 1H), 2.88-2.54 (m, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H). 13C-NMR (75 MHz, CDCl3): 186.7, 168.5, 160.5, 147.1, 146.4, 142.9, 141.6, 140.7, 130.4, 129.8,

121.7 (2C), 120.0, 117.8, 117.1, 113.5, 102.2, 61.7, 61.4, 60.3, 59.8, 58.9, 54.6, 41.6, 36.9, 29.7, 24.1, 20.3, 15.8, 14.1, 9.6. ESI-MS m/z: Calcd.. for C31H31N3O9S: 621.7. Found (M+H)+: 622.2.

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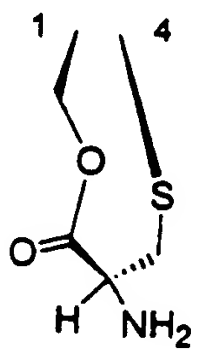
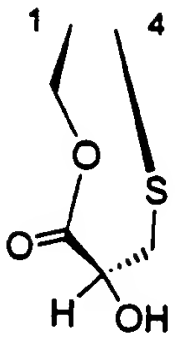
CLAIMS

1. A compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



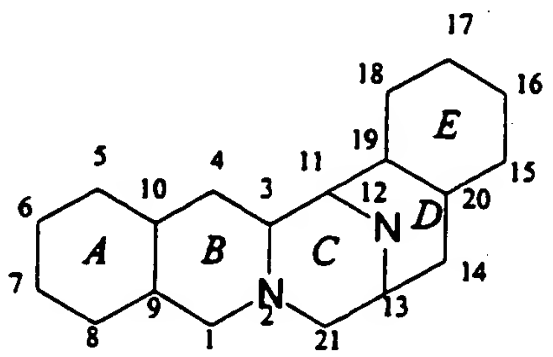
VIa



VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583 or 597, and with the exception of compounds 14, 15 or 47 of U.S. Patent No 5,721,362.

2. A compound according to claim 1, wherein the fused ecteinascidin five ring system is as in the ecteinascidins, the ring system being of the formula (XIV):



Where the rings A and E are phenolic; the rings B and D are tetrahydro, and ring C is perhydro.

3. A compound according to claim 2, wherein substituents at positions 5, 6, 7, 8, 12, 16, 17, 18 and 21 are as in a known ecteinascidin.

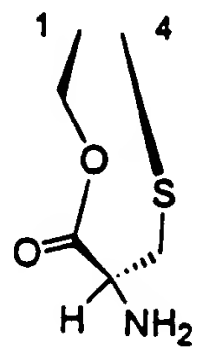
4. A compound according to claim 3, wherein the substituents at positions 5, 6, 7, 8, 12, 16, 17 and 18 are as in a known ecteinascidin.

5. A compound according to claim 3 or 4, wherein the known ecteinascidin is ecteinascidin 743.

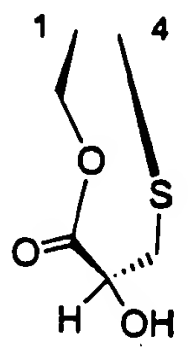
6. A compound according to any preceding claim, wherein the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised.

7. A compound according to claim 6, in which the group $-CHNH_2-$ in the 1,4 bridge is replaced by a group $-C(X_2)_2-$, where X_2 is OX_1 or $N(X_1)2$ wherein the or each X_1 is independently H, $C(=O)R'$, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl, or two X_1 groups may together form a cyclic substituent on the nitrogen atom.

8. A pharmaceutical composition comprising a compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



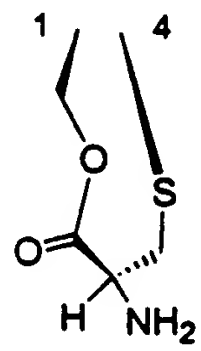
VIa



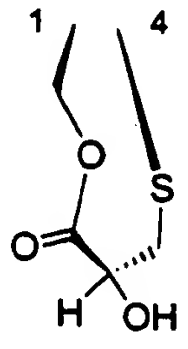
VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583 or 597, together with a pharmaceutically acceptable carrier.

9. The use of a compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



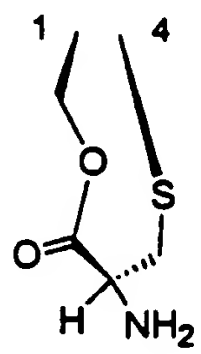
VIa



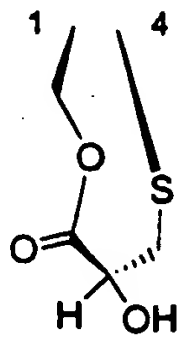
VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583 or 597, in the preparation of a medicament for use in the treatment of a tumour.

10. A method of treating a tumour which comprises administration of an effective amount of a compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



VIa



VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583 or 597.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01667

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D515/22 A61K35/00 A61K35/56 //(C07D515/22,317:00, 291:00,241:00,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 721 362 A (COREY ELIAS J ET AL) 24 February 1998 (1998-02-24) cited in the application claims 1,29-31; examples 14,1547	1,7,9
X	E.J.COREY,DAVID Y.GIN, AND ROBERT S. KANIA: "Enantioselective Total Synthesis of Ecteinascidin" J.AM.CHEM.SOC., vol. 118, 1996, pages 9202-9203, XP002925428 page 203; examples 14,15; table 1A	1,7

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 July 2001	11/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016	Goss, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/GB 01/01667

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RYUICHI SAKAI ET AL.: "Ecteinascidins: Putative Biosynthetic Precursors and Absolute Stereochemistry" J.AM.CHEM.SOC., vol. 118, 1996, pages 9017-9023, XP002925426 page 9023, left-hand column, paragraph 1; examples 1-4	1,7
A	FUKUYAMA, LIHU YANG, KAREN L.AJECK: "Total Synthesis of(+)-Saframycic" J.AM.CHEM.SOC.,, vol. 112, 1990, pages 3713-3715, XP002925425 the whole document	1,9
A	THORU FUKUYAMA ET AL.: "Stereocontrolled Total Synthesis of Saframycic B" J.AM.CHEM.SOC., vol. 104, 1982, pages 4957-4958, XP002925427 the whole document	1,9
A	J.W.LOWN, ALUMMOOTTIL V.JOSHUA ET AL.: "Molecular Mechanisms of Binding and Single-Strand Scission of Deoxyribonucleic Acid by the Antitumor Antibiotics saframycic A and C" BIOCHEMISTRY, vol. 21, no. 3, 1982, XP002925424 the whole document	1,9

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]nal Application No
PCT/GB 01/01667

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5721362 A	24-02-1998	AU 4420597 A	14-04-1998
		CN 1237974 A	08-12-1999
		CZ 9900914 A	11-08-1999
		EP 0931083 A	28-07-1999
		HU 0000068 A	28-06-2000
		JP 2001501196 T	30-01-2001
		NO 991301 A	14-05-1999
		PL 332206 A	30-08-1999
		WO 9812198 A	26-03-1998

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* WPP82129

Box No. I TITLE OF INVENTION

ANITITUMORAL ECTEINASCIDIN DERIVATIVES

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E 28760,
Spain

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Ruffles, Graham Keith
57-60 Lincoln's Inn Fields,
London, WC2A 3LS,
United Kingdom

This person is:

☒ applicant only

☐ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Ruffles, Graham Keith
Marks & Clerk
57-60 Lincoln's Inn Fields,
London, WC2A 3LS,
United Kingdom

Telephone No. 020-7400-3000

Facsimile No. 020-7404-4910

Teleprinter No. 25311 EMANDC G

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Flores, Maria
Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E-28760,
Spain

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of:
☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Francesch, Andrés
Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E-28760,
Spain

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of:
☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Gallego, Pilar
Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E-28760,
Spain

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of:
☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Chicharro, Jose Luis
Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E-28760,
Spain

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of:
☐ all designated States
☐ all designated States except the United States of America
☒ the United States of America only
☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Zarzuelo, Maria
Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E-28760,
Spain

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Fernández, Carolina
Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E-28760,
Spain

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
Manzanares, Ignacio
Pharma Mar, S.A.
Calle de la Calera 3
Poligono Industrial de Tres Cantos
Tres Cantos,
Madrid, E-28760,
Spain

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ES

State *(that is, country)* of residence: ES

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
☐ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AG** Antigua and Barbuda
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
☒ **BY** Belarus .....
☒ **BZ** Belize .....
☒ **CA** Canada
☒ **CH and LI** Switzerland and Liechtenstein
☒ **CN** China .....
☒ **CR** Costa Rica .....
☒ **CU** Cuba .....
☒ **CZ** Czech Republic .....
☒ **DE** Germany .....
☒ **DK** Denmark .....
☒ **DM** Dominica
☒ **DZ** Algeria .....
☒ **EE** Estonia .....
☒ **ES** Spain .....
☒ **FI** Finland .....
☒ **GB** United Kingdom
☒ **GD** Grenada
☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
☒ **HR** Croatia .....
☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
☒ **MN** Mongolia
☒ **MW** Malawi .....
☒ **MX** Mexico .....
☒ **MZ** Mozambique
☒ **NO** Norway
☒ **NZ** New Zealand .....
☒ **PL** Poland .....
☒ **PT** Portugal .....
☒ **RO** Romania
☒ **RU** Russian Federation .....
☒ **SD** Sudan
☒ **SE** Sweden
☒ **SG** Singapore
☒ **SI** Slovenia .....
☒ **SK** Slovakia .....
☒ **SL** Sierra Leone .....
☒ **TJ** Tajikistan .....
☒ **TM** Turkmenistan .....
☒ **TR** Turkey .....
☒ **TT** Trinidad and Tobago .....
☒ **TZ** United Republic of Tanzania
☒ **UA** Ukraine .....
☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
☒ **VN** Viet Nam .....
☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
☒ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ CO Colombia .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Ruffles, Graham Keith is co-applicant for Sudan ONLY.

The applicant additionally designates any PCT contracting state not listed in Box No.V

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 12 Apr 2000 (12.4.00)	0009043.1	GB		
item (2) 15 May 2000 (15.5.00)	PCT/GB00/01852	GB (PCT)		
item (3) 14 Sep 2000 (14.9.00)	0022644.9	GB		

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1);(2);(3)

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 6
description (excluding sequence listing part)	: 113
claims	: 3
abstract	:
drawings	: 1
sequence listing part of description	:
Total number of sheets	: 123

This international application is **accompanied** by the item(s) marked below:

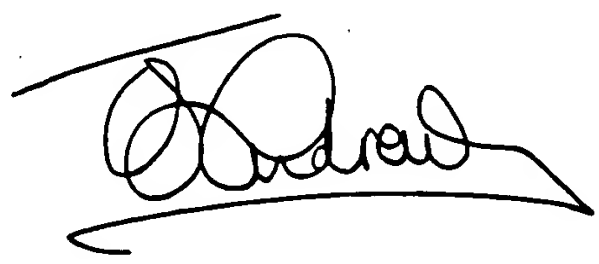
1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other *(specify)*: Form 23/77 X3

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).



For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: WPP82129

Applicant: Pharma Mar, S.A., et al

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 55 T

2. SEARCH FEE . . . . . 624 S

International search to be carried out by _____

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 123 sheets.

first 30 sheets 264 b1

6 (remaining sheets) x 93 (additional amount) = 558 b2

Add amounts entered at b1 and b2 and enter total at B . . . . 822 B

Designation Fees

The international application contains 89 designations.

6 (number of designation fees payable *(maximum 6)*) x 56 (amount of designation fee) = 336 D

Add amounts entered at B and D and enter total at I . . . . . 1158 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 66 P

5. TOTAL FEES PAYABLE . . . . . 1903 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☐ authorization to charge deposit account (see below)
- ☒ cheque
- ☐ postal money order
- ☐ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☐ other *(specify):*

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____

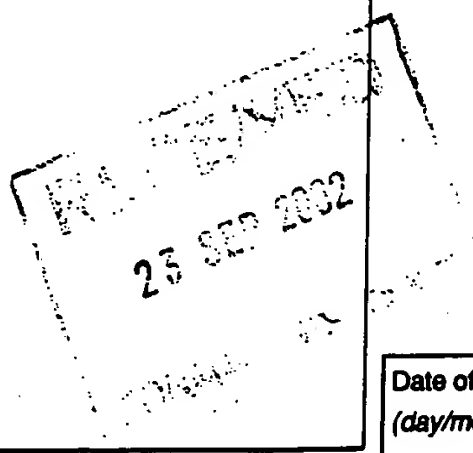
- ☐ is hereby authorized to charge the total fees indicated above to my deposit account.
- ☐ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No. | Date *(day/month/year)* | Signature

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Ruffles, Graham Keith
MARKS & CLERK
57-60 Lincoln's Inn Fields
London WC2A 3LS
GRANDE BRETAGNE



PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.09.2002
Applicant's or agent's file reference WPP82129	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB01/01667	12/04/2001	12/04/2000

Applicant
PHARMA MAR, S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Neubauer, M Tel.+49 89 2399-7272

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
WPP82129		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB01/01667	12/04/2001	12/04/2000
International Patent Classification (IPC) or national classification and IPC C07D515/22		
Applicant PHARMA MAR, S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/11/2001	20.09.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Goss, I Telephone No. +49 89 2399 8292

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB01/01667

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-13 as originally filed

Claims, No.:

1-10 as received on 06/11/2001 with letter of 31/08/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 10.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	

No: Claims 1-10

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claim 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
The following documents cited in the Search Report are referred to in this IPER:

D1: E.J.COREY,DAVID Y.GIN, AND ROBERT S. KANIA: 'Enantioselective Total Synthesis of Ecteinascidin' J.AM.CHEM.SOC., vol. 118, 1996, pages 9202-99203, XP002925428

D2: US-A-5 721 362 (COREY ELIAS J ET AL) 24 February 1998 (1998-02-24) cited in the application

D3: FUKUYAMA, LIHU YANG, KAREN L.AJECK: 'Total Synthesis of(+)-Saframycic ' J.AM.CHEM.SOC.,, vol. 112, 1990, pages 3713-3715, XP002925425

D4: THORU FUKUYAMA ET AL.: 'Stereocontrolled Total Synthesis of Saframycic B ' J.AM.CHEM.SOC., vol. 104, 1982, pages 4957-4958, XP002925427

D5: J.W.LOWN, ALUMMOOTTIL V.JOSHUA ET AL.: 'Molecular Mechanisms of Binding and Single-Strand Scission of Deoxyribonucleic Acid by the Antitumor Antibiotics saframycic A and C' BIOCHEMISTRY , vol. 21, no. 3, 1982, XP002925424

D6: RYUICHI SAKAI ET AL.: 'Ecteinascidins: Putative Biosynthetic Precursors and Absolute Stereochemistry' J.AM.CHEM.SOC., vol. 118, 1996, pages 9017-9023, XP002925426

Clarity

Claim 1 is formulated in an unclear manner and the basic skeleton of ecteinascidin of general formula (XIV) according to claim 2 must be taken into claim 1 as well as the vague term "derivatised" must be specified by the meanings given in the description as otherwise it is not possible for the skilled reader to establish the extent of f te protection. Also claim 7 is lacking clarity; no support could be found in the compounds exemplified for either group $-C(X_2)_2$ or $N(X_1)_2$.

In Claims 3, 4 as well as 5 the substituents are simply defined by a reference to the known ecteinascidin substituents. Applicant's attention is drawn to the fact that the matter for which protection is sough must be defined in a clear and concise manner and in respect of the technical features of the invention, and the claims must not rely on references to the description, drawings or examples except where absolutely necessary.

Novelty

Many compounds with a ring structure of formula (XIV) having a 1,4 bridge of formula VIA or VIB according to claim 1 and 2 are known from the prior art as already anticipated in the passages quoted in the search report.

Actually both claims 1 and 2 are so extremely vague defined that all possible conceivable systems with respect to the oxidation pattern of the aromatic rings, the nature of the substituents as well as the presence of further condensed ring(s) are included within the claimed scope. The compounds according to the passages quoted in the search report are falling within this general definition of the subject-matter claimed.

All the dependent claims thereupon do not appear to offer any further relevant technical feature(s) of the invention which could be recognized as being indeed novel. The applicant is kindly reminded that the novelty rendering feature must be shared by all the class of compounds claimed (unity of the invention) and responsible for the activity of the claimed compounds with regard to the very close related prior art.

Novelty cannot be recognized.

Inventive step and industrial applicability

Since the subject-matter presently claimed does not satisfy the requirements for novelty, a final opinion on both inventive step as well as industrial applicability cannot be given. However following should be remarked:

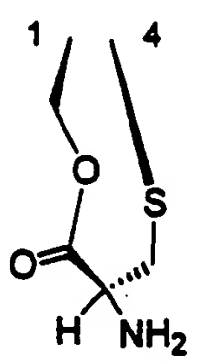
a) the compounds claimed are not clearly distinguished from those already known which are also disclosed to have antibacterial and other useful properties.

b) No surprising or better effects have been shown for the very broad family of compounds claimed so that also the technical usefulness cannot be regarded as the unexpected technical common link on which basis the inventive step of the claimed matter could be evaluate.

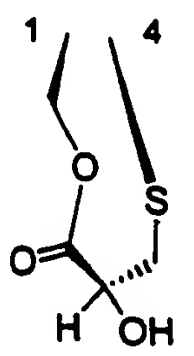
c) Moreover also in view of the complexity of the stereochemistry of the compounds involved (stereochemistry which has an important role in the DNA binding (see D4, figs.9 or 10) the way of carrying out the invention must be disclosed in a manner sufficiently clear and complete for the person skilled in the art.

CLAIMS

1. A compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



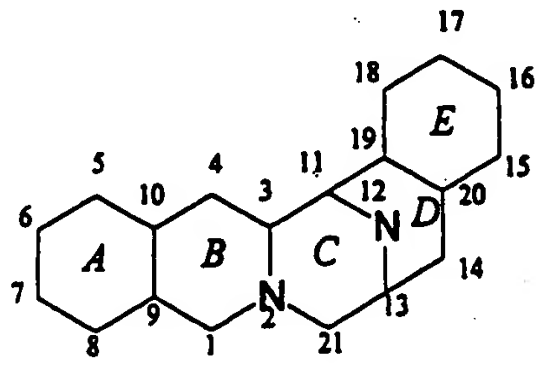
VIa



VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583, ecteinascidin 597 or N-acetylecteinascidin 597, and with the exception of compounds 14 or 47 of U.S. Patent No 5,721,362.

2. A compound according to claim 1, wherein the fused ecteinascidin five ring system is as in the ecteinascidins, the ring system being of the formula (XIV):



Where the rings A and E are phenolic; the rings B and D are tetrahydro, and ring C is perhydro.

3. A compound according to claim 2, wherein substituents at positions 5, 6, 7, 8, 12, 16, 17, 18 and 21 are as in a known ecteinascidin.

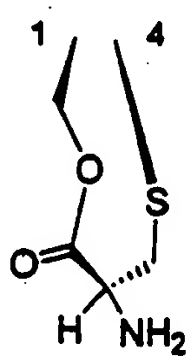
4. A compound according to claim 3, wherein the substituents at positions 5, 6, 7, 8, 12, 16, 17 and 18 are as in a known ecteinascidin.

5. A compound according to claim 3 or 4, wherein the known ecteinascidin is ecteinascidin 743.

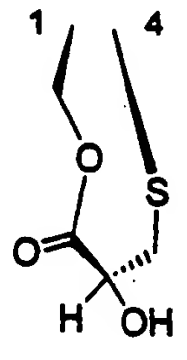
6. A compound according to any preceding claim, wherein the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised.

7. A compound according to claim 6, in which the group $-CHNH_2-$ in the 1,4 bridge is replaced by a group $-C(X_2)_2-$, where X_2 is OX_1 or $N(X_1)2$ wherein the or each X_1 is independently H, C(=O)R′, substituted or unsubstituted C_1-C_{18} alkyl, substituted or unsubstituted C_2-C_{18} alkenyl, substituted or unsubstituted C_2-C_{18} alkynyl, substituted or unsubstituted aryl, or two X_1 groups may together form a cyclic substituent on the nitrogen atom.

8. A pharmaceutical composition comprising a compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



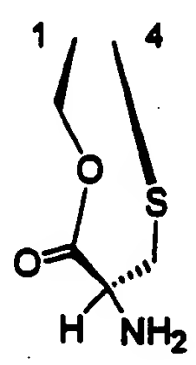
VIa



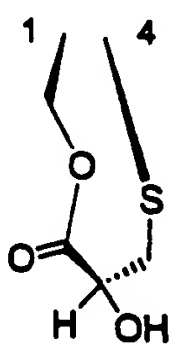
VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583 or 597, together with a pharmaceutically acceptable carrier.

9. The use of a compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



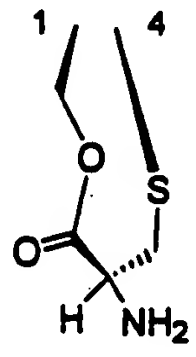
VIa



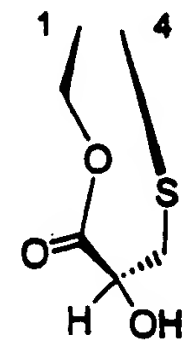
VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583 or 597, in the preparation of a medicament for use in the treatment of a tumour.

10. A method of treating a tumour which comprises administration of an effective amount of a compound having a fused ecteinascidin five ring system with a 1,4 bridge having the structure of formula (VIa or VIb):



VIa



VIb

and compounds in which the $-NH_2$ or $-OH$ of the 1,4 bridge is derivatised; with the exception of ecteinascidin 583 or 597.